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## UNDERGRADUATE INSTRUCTION IN TUBERCULOSIS.[1]


By Allen K. Krause.

*(From the Kenneth Dows Fund for the Study of Tuberculosis, of the Medical Clinic of The Johns Hopkins Hospital.)*


I should like to make a thorough investigation of undergraduate instruction in tuberculosis, because I think the subject deserves it and demands it; but the limits of this paper forbid this. I shall therefore confine myself to the exposition of a few matters as I see them, imperfectly perhaps, incompletely and with no gray hairs of experience behind me; yet, withal, with honesty I trust and a consuming desire to help and do my share.

Tuberculosis teaching in our medical schools is an unsolved problem. It demands attention and more active consideration than the passing of resolutions in committee meetings. I believe its solution to be the most pressing one before us to-day. Have you ever stopped for a moment to consider what it would mean if every year every one of our several thousand graduates in medicine left school with some interest in tuberculosis, with some idea of how to make a diagnosis, with some judgment of what to do with the patient once he labelled him? What do you think would be the situation if fifty years from now every practising physician appreciated the relations between infection and disease, the relative value of signs and symptoms, the importance of the practice of conservative medicine on those who reacted tuberculously but were not tuberculously ill—the pregnant woman, the man with a common cold, the child with measles, the patient about to undergo a serious surgical operation? What, if in thinking of tuberculosis every physician's instinct immediately sensed curability of infection, arrest of disease and recrudescence of clinical arrest? What, if his social sense at once responded to the fact that in nine cases out of ten tuberculosis bankrupts, that the disease leaves *young* widows with *young* children, that its victims spread infection for years as against the months of the syphilitic, that syphilis hampers while tuberculosis disables, that cancer meets the man after he has arrived, whereas tuberculosis strikes him down as he is beginning the race? What, if throughout the land we had all these men, these foci, who have real knowledge and therefore real interest, who have their fortuned patients and their honest derelicts, in whom the rich confide and on whom the poor de-

[1] Read before the Clinical Section of the Thirteenth Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, Cincinnati, Ohio, May 11, 1917.

pend, who could so well arouse Dives to come to the aid of Lazarus? All this is common knowledge among specialists. Can it not be made available to our students?

It can. The material to work on is at hand in every medical school where the student can get a glimpse at the sick and the dead, at the autopsy table and the microscope. Everywhere there is the person who harbors tubercle yet is not ill with tuberculosis, the man who runs the gamut of physical examination before a diagnosis of tuberculosis can be accepted or ruled out, the consumptive who makes his own diagnosis. Everywhere there is the patient whose management you must arrange, the man who once had tuberculosis but who is now well rid of it, the "cure" who returns, again broken down and discouraged. In every clinic, no matter how primitive, you will see the face tighten and you will listen to the despairing tones as you give your opinion, to the story of the lost livelihood, of the dependent relatives, of the black economic outlook. No medical school can say that it is too poor to teach tuberculosis. It can no more escape the ubiquity of the tubercle bacillus than can the cabin in the city alley.

Now it has been said that even although the facilities to teach tuberculosis are given, the medical student has no interest in the subject and cannot be interested. This I do not believe, and I cannot help thinking that the affirmation too often shifts the burden of reproach from the teacher, where it belongs, to the student. It cannot be denied that the American medical student is awake to everything that is interesting or is presented in an interesting manner. Nor can it be gainsaid that nothing so lends itself to lively and living exposition as tuberculosis. Of course, a good deal depends on what we mean by tuberculosis. A drab, relentless routine of percussion of pale and sickly patients and of sentence to the same grind of treatment will no doubt discourage many a student and leave him cold. But tuberculosis as a subject for study, as a subject for teaching—what more can any man want? Tell me anything that offers so great and so unique an opportunity to both student and teacher as tuberculosis, which ever since men began to live together has entered so largely, so intimately, so dreadfully into their lives. Tuberculosis: a disease of every part of the earth, of every historical era and of every race; a disease of infancy, of adolescence and of old age; a disease that exerts its effects on every organ and tissue of the body, that may be isolated or may be wide-spread or may take on almost every conceivable combination; that may come like the lightning stroke or more insidiously than the advance of age itself; that may kill in a week or drag out its career through a normal life span, a lazy career perhaps, perhaps a checkered one, but never a colorless one; a disease, too, whose active cause is known and is scarcely less interesting or less versatile than the effects it produces—how wonderful is this trinity of bacilli, human, bovine, avian, so like and yet so unlike; how wonderful their less combative cousins, the saprophytic acid-fasts! And if we would go on and enumerate other attributes—the universality of infection, the indifference of the germ to the portal of entry available, its armor against the body's weapons, its habits of hibernation and rejuvenescence, its triumphs as we read the roll of victims—and there are both quantity and quality there—and as we proclaim it captain of the hosts of crushed ambition and of death; when we consider the imitations of almost every other malady that it paints and how it leads us through the realms of all medicine if we would tag it; when, in addition, we consider how often and how much it leans on other diseases and on the habits and constitution of man to exert its effects, then we would ask, "What then would a man rather study, what rather teach than tuberculosis?" Laennec and Louis and Virchow and Cohnheim and Austin Flint and Trudeau are inspiring enough and good enough company for any man.

In planning tuberculosis teaching there will probably never be complete agreement of opinion as to the curriculum and the personnel of the teaching staff. It is only natural that the dispensary, the wards of the general hospital, the laboratory or the sanatorium, in turn, should be emphasized by men whose interests and activities lie in any particular field. Tuberculosis itself is breaking up into a number of specialties, and the men who single-handed can present the subject in an adequate and well-rounded manner are very few indeed. There are those who look upon the diagnosis of early disease as the heart of our present problem. There are others who believe systematic segregation of the open case to be the essential point of attack. There are some who declare frankly that there can be no solution until the discovery of some therapeutic agent that will cure practically every variety of case. There are not a few who are convinced that at bottom the problem is an extramedical one, that its roots are embedded and flourish in the bed-rock and top-soil of our present-day civilization which is the flower of ages of evolution and social conventions, and that nothing less than a slow, laborious and complete revolution or development of social habits and customs can effect a radical change in the situation. In our dilemma it is likely that, as always, Truth is many-sided, and that no one man or group of men has a monopoly of wisdom, and that if we are to impart our available information to our students we must correlate in a practical way the abilities and efforts of a number of men working in particular fields.

This, you will say, is nothing else than a repetition of a general medical course applied to a special subject and involves more time than can be devoted by the medical undergraduate. It is indeed a wheel within a wheel, and for a few minutes I wish to detail how such a plan is feasible and practical. And understand, that since I believe that tuberculosis will play a larger part in a practitioner's professional life than any other disease, I do not think that we need be backward in asking our medical faculties for all the time that they can allot to the subject.

As matters stand now, the student, even though no formal course in tuberculosis is offered, really sees a good deal of tuberculosis and hears a good deal about it during his four years in the medical school. During his course in pathology and in every general and special clinic he sees a variety of tuberculous conditions and hears their nature, their diagnosis and their treatment discussed. But as a rule they are here pre-

sented as incidents, as isolated and individual affections, and except by the unusual man their broader aspects, their relations and their points of contact and contrast as regards tuberculosis at various stages, locations, time of infection, immediate cause of disease, etc., are scarcely touched upon. In the general and special clinic, tuberculosis is taken up in an incidental and not a systematic manner. It is an occurrence that flashes across every day's routine and is very properly handled as such. The result is that the student picks up some very valuable points of diagnosis and, if he is receptive, carries away the accepted method of treatment. But his idea of tuberculosis is not enlarged and he may see hundreds of cases without getting the first fundamental conception of the life history of the individual case (not patient) of tuberculosis, the conception that in almost every instance clinical tuberculosis is the fruition of a seed implanted in the obscure past, nourished, blighted and again nourished by all the vital incidents that have entered into the physical life of the individual.

It is of the utmost importance, however, that the internist, the surgeon, the laryngologist, the pediatrician, the orthopedist, the urologist, continues to teach tuberculosis as he is doing at present. But it is very necessary that we supplement this instruction by some systematic and correlated course in tuberculosis: a course that is all tuberculosis, that selects its material from the other fields of medicine and weaves it all into an orderly, consistent fabric, the warp and woof of which are tuberculosis, the technical threads of which are refined and polished, and the cloth ready to be made into a fit garment when the occasion arises.

Such a course should aim to interpret and correlate systematically all that the student has seen or is likely to see in his contact with all kinds of tuberculous patients. Besides this, it must be based on a clear idea of what the requirements of the situation are, what is most worth while to the student and what will most contribute to the advancement of the anti-tuberculosis movement. It must not spend itself in an aimless recital of physical signs and symptoms and of the management of the patient. It must have a proper sense of proportion and proceed along lines that take into account the relative weight and emphasis to be given to the various phases of what has come to be known as the tuberculosis problem.

Fully aware that I at once lay myself open to contradiction and disagreement, I would enumerate in the order of their relative importance the things that should be taught the student, as follows: First, the importance of *not* making a diagnosis of tuberculosis; second, some rational idea of what to do with the patient once he has been called tuberculous; third, the relapsing nature of the malady; fourth, some conception of the relative value of signs and symptoms in evaluating the individual case and a firm and lasting impression that no disease is quite so notorious as tuberculosis in disharmony of anatomic change, physical signs and symptoms; fifth, the fact that every tuberculous patient must be handled strictly as a personal entity and his course directed only after full and complete knowledge of his family, social and economic conditions; sixth, the technique of making a diagnosis. You will at once see that several of these phases cannot be sharply cut off one from the other and that they overlap. I assume that the student has had an elementary course in general pathology and that he has had bred into him the habit of applying his pathological senses to all clinical manifestations that he may encounter, although here also I would take up tuberculosis in its special manifestations. If you will refer to the list that I have just outlined, I believe that you will agree that in general its arrangement corresponds with the difficulty and length of time it took us to acquire our own experience of any particular aspect.

To put the matter briefly and sharply, our teaching problem is to give our students the broadest and most practical view of tuberculosis in the shortest possible time and with the least interference with his other courses. He must begin clinical acquaintance with the disease in his third year. He should receive instruction in it in connection with all his other clinical courses, for this will constantly breed into him the instinct of the universality and the innumerable ramifications of tuberculosis. He should in addition be given the opportunity to study tuberculosis in a formal and well-formulated manner and be taught by men whose experience has shown them what to present and how to present it. The material to work on is everywhere abundant, but in too many places the necessary organization and facilities are lacking.

The necessary tools are a tuberculosis dispensary, an adequate laboratory (though it is remarkable how much can be accomplished with a thermostat, a centrifuge and a modicum of glassware) and an able and enthusiastic teaching force. A most helpful adjuvant is a tuberculosis ward. I do not, however, consider the ward as necessary to the undergraduate student, though it may be very valuable to the teacher and advanced student. The first and main impression that the beginning student of tuberculosis should get is the right impression, and to get the right impression of tuberculosis one must become familiar with it in its environment. I would therefore recommend that the student do a certain amount of out-patient work; in fact, I consider this almost necessary for a proper appreciation of the disease. I cannot see how the undergraduate will pick up in the tuberculosis ward anything of prime importance that he cannot just as well get in the dispensary or in the home. As a matter of fact, too much acquaintance with ward patients at the beginning may give him the wrong impression, for here he would work only with diagnosed patients; and the consumptive lying in a clean bed in a bright room and receiving the best of care is not the usual picture of the disease.

In the dispensary, of course, the student will first meet the man who walks in because he isn't feeling just as he should. He will form his acquaintance and listen to his story and record it. He will be taught the great importance of a medical and social history, particularly in such a patient. He will make a physical examination of the man and record what he has found. In company with the dispensary physician and teacher he will study the case. He will be intensively instructed in the technique and mechanics of physical diagnosis.

He will take the patient's sputum and other specimens to the laboratory and examine these himself. He will look into the patient's home life and occupation or will have it reported to him by the dispensary nurse. He will discuss the patient's management with the dispensary physician, and here we shall leave the individual student for a while.

To get the best results, results that are best for the student, teacher and patient, only a few students, three or four, should work in the ordinary dispensary at a time. But matters should be so arranged that every student spends at least 32 hours, that is, two hours a day twice a week for eight weeks, in the dispensary. In this time he can fall in with a good variety of patients and can acquire some slight facility in percussion and auscultation of the chest. He should at least have acquired some sense of his own limitations. And this leads me to the matter of diagnosis in general and of early diagnosis in particular.

I won't say that the majority, but I will say that many cases of pulmonary tuberculosis need no physical examination for diagnosis. As a rule, the patient's associates at home can diagnose what we call consumption. In a great many other cases sputum examination (and it is not practised enough or often until days, and perhaps weeks, have been spent in elaborate chest examinations) will proclaim the condition. But it is remarkable how much scolding we physicians have had from extremists of the early diagnosis school. We would almost gather from some brochures that, if he had been alert enough and keen enough and not too ignorant, every physician might have saved every consumptive's life had he picked up the disease at its first flicker. I realize that the purpose of these propagandists is most worthy, though I do not believe that early diagnosis deserves the importance in the tuberculosis firmament that some would give it. Trying my best to know and understand conditions that exist, I consider it only a minor arm of the service in our battle. All this when I realize that in so many instances patients with insidious tuberculosis first consult the physician only after the malady is well expressed and that in so many others the disease begins abruptly and acutely in a way that cannot be considered incipient in point of extent of lesion and symptoms.

Now just because of this warped and narrow vision of tuberculosis it has come about that in his course the student only too often has got the idea that the detection of the ultimate râle is about all there is to tuberculosis, and he promptly proceeds to polish off his technique so that he can compete in the game. He has also heard of milk and eggs, and equipped with the knowledge that persistent, localized râles after coughing so often mean tuberculosis, and with a hazy belief in the potency of milk and eggs, and profoundly ignorant that there are things like symptoms and medical history and individual habits to be considered, he goes out to snare his tuberculous patient. This is the situation that I protest and I do it with the fullest respect for early diagnosis in its place and believe absolutely that training and proficiency in physical examination is the very corner-stone of medical diagnosis. But I sometimes wonder whether all the tragedies resulting from failure to diagnose early have not been more than atoned for by the tragedies of a false diagnosis of tuberculosis. Therefore, the first deep tract that I would lay down in the student's brain is one that ever warns him never to make a diagnosis of pulmonary tuberculosis unless he can prove it. He may have his opinion and he may have his patient undergo what is substantially treatment for tuberculosis, but he should not voice a flat opinion to the patient nor should he send him to a tuberculosis resort.

All this analysis of history and signs and symptoms can be taken up in the dispensary with the student, who should not leave the medical school without acquiring a sense of proportion that is well balanced and which he can put into practice. It is in the dispensary that the student must get method and data and some point of view. But in addition to this he must have his point of view clarified, broadened and well grounded.

This enlargement and strengthening of vision is to be done by clinics and by lectures. In eight or nine clinics and ten or a dozen lectures a great deal can be accomplished. The clinics should be well ordered and proceed from one to the other in a developmental manner. Not too much emphasis should be paid to the eliciting of signs, as these can be best worked over in the dispensary. But an effort should be made to present as many people as possible to the student and in an interesting manner to recite the past and present history of these people. Beginning with a display of children whose skins do not react to tuberculin, we can then show some that do but who have never had clinical tuberculosis. We can then go on to those who are now in the best of health but who have a history of one or more attacks behind them. We can exhibit children who are for the time being ill with tuberculosis. We can meanwhile take the opportunity to discuss contact, methods of infection, latency, types of disease, and in general contrast the situation in the child with that in the adult.

Our next clinics would take up the adult. Pulmonary disease is now the type. We may present healthy men who have put severe disease behind them. We show acute tuberculosis and chronic tuberculosis and the combination of these. We show the disease that began with hæmoptysis, that with onset with cough and expectoration or with pain or with transient, daily lassitude. We discuss the significance of symptoms, the technique of laboratory diagnosis, the balancing of history and signs and symptoms, the amelioration of symptoms, the relapse after arrest, the method of treatment and the ultimate prognosis. All these nine clinics should be so arranged that, beginning at the first clinic with infection without clinical disease in the child, we proceed step by step to a demonstration of prognosis in the adult and prophylaxis in the last clinic. And throughout all of them an effort should be made to bring into harmony what the student has seen in the other services of the hospital and to give each manifestation its proper place.

The student is now ready to take up tuberculosis in its broadest aspects. Following the clinics he should be given a course of about a dozen lectures that would deal with such matters as the pathology of tuberculosis, the place of the disease in the history of medicine, the history and attributes of

the tubercle bacillus, the factors that influence infection, the development and effects of infection, the conversion of infection into disease, the spread and arrest of disease, the nature and effects of tuberculin, hypersensitiveness and immunity, therapy, prognosis, prophylaxis and the social side of tuberculosis. The aim of such lectures should be not so much to stress the obvious as to guide and arouse the student and to prepare him to handle his future acquaintance with tuberculosis in a rational and logical manner.

Now all of this dispensary, clinic and lecture instruction can be given during the third year with a maximum of about 50 hours of attendance. The dispensary work is mainly to develop method; the clinics and lectures are largely orienting and interpretative. The student goes to his work in the other services of the medical school immeasurably better prepared to appreciate all the cases of tuberculous disease that he may encounter. Additional instruction that might be arranged would be joint clinics held by the teacher of tuberculosis and the pediatrician, the orthopedist, the laryngologist, the ophthalmologist, the roentgenologist or the surgeon. That such a course in tuberculosis is not an unattainable ideal is evidenced by the fact that it is to-day being carried out in most of its details in one of our medical schools.

Besides the required work that has been outlined above, other opportunities should be offered those students who have the time and inclination to make use of them. In the laboratory there should always be a few desks available where the selected fourth-year student can begin the study of the special bacteriology, serology and clinical microscopy of tuberculosis and can take up the simpler methods of animal experimentation. Such elective courses are, however, hardly worth while unless the student's course is so arranged that he can devote three or four consecutive hours a day two or three times a week over a period of one-third of the scholastic year. Unless the laboratory facilities are very unusual, not more than two or three students a year should be allowed to elect such work.

The out-patient work of the dispensary is capable of great development and should be utilized to better advantage. It is of the utmost importance that we devise some method whereby the student can get a consecutive view of the progress of a case of tuberculosis. In no other way will he have quite so good an opportunity to become familiar with and gain an appreciation of the ups and downs of the average patient. If he can follow intimately one or several cases over a period of months or a year or two, he will gain a valuable and lasting impression of the pendulum-like progress and decline of the ordinary tuberculous patient, and under proper guidance may learn lessons that otherwise might take him years to acquire in practice. We have, therefore, called for volunteers from our third-year students, who for the remainder of their medical course pledge themselves to visit dispensary and discharged sanatorium patients. We plan to have them undertake toward these patients the shadow or even the reality of the family physician. They will be under the supervision and guidance of the dispensary physicians and the visiting nurse. We aim to emphasize the human relation between attendant and patient. We put the matter to the patient frankly; we want to help him, we are not planning to do any detective work; we want to prevent relapse, we are trying to give him a better chance of ultimate and lasting recovery from his disease; we want him to make a friend and a confidant of our student. The student on his side now has a rare opportunity to learn a great deal about real tuberculosis and, as he frequents the home of the dispensary patient, he also begins to learn something about the ultimate problem of the conquest of tuberculosis, something that makes a lasting impression and which will give him no small impetus when he begins his medical practice. We for our part can keep better track of some of our dispensary patients and can do a good deal of social service work at a minimum of expense. Although the details of this plan have not been worked out, I am confident that it is workable and that it is capable of great development. I am also sure that there will be no dearth of volunteers from the student body.

In the dispensary work the effort should be made to give the student as intensive a training in physical diagnosis as the time and the facilities allow. But it is obvious that even under the best conditions the student cannot become a finished examiner with 32 hours of work. As in everything else, the only way to learn physical examination is to practise it, and it is highly desirable that some arrangement be made whereby the student who desires to go further into tuberculosis will have the chance to work among large numbers of patients. In this connection a ward in a hospital would be valuable, for here several advanced undergraduates might always have the opportunity to perfect themselves in physical diagnosis. But it seems to me that a better plan would be to enlist the coöperation of the tuberculosis sanatoria.

It has been frequently stated that the medical staffs of our sanatoria are undermanned, and that it is difficult to interest in this work men who have not had tuberculosis themselves. Why would it not be a good plan for the sanatoria to use our third and fourth year students as clinical clerks or internes during the summer vacations? For three or four months the student would be assisting in the institutional work. He would make frequent examinations of a great many patients of various types. He could do part of the clinical laboratory work and sometimes carry on a small piece of original research. He would relieve the permanent resident staff of a great deal of routine work and thus give the residents more time for study and investigation. He would himself be gradually absorbing a point of view of tuberculosis that he could get in no other way and learn much about the systematic and disciplinary treatment of the tuberculous. At the same time the ambitious student, worn perhaps after a year's hard work in the medical school, would be supplementing his course in surroundings that would be attractive and would physically benefit him more than the same length of time spent in the hot and dusty city. The sanatorium is bound to get a good deal from the student, but it must also give something in return. It should provide full maintenance for the student. It must not make an orderly out of him, nor simply fill his day's routine with mere drudgery that the residents are glad to be rid of. As a rule, the student

will come ready to work and very anxious to learn. The sanatorium must take enough personal interest in him to see to it that he is taught. This plan is already being tried by Dr. D. A. Stewart of Manitoba, and I believe it capable of great development. To be most effective it should be used as advanced training, that is, for those students who have already had some clinical experience and formal instruction in tuberculosis. It should be for the man who elects it, the man who shows a voluntary interest in the subject.

This sketch of a course of instruction in tuberculosis has been evolved with but one idea in view. It aims to be practical, to make use of conditions such as exist at most medical centers. If any particular clinic is blessed with an ideal equipment and facilities, then that is another matter and we would outline what might perhaps be an ideal course. But I think that it is a great mistake to wait for the arrival of big things before attempting to do anything and in an organized and systematic manner to make use of what is at hand. The use of dispensary patients, a small clinical laboratory, coöperation with other services and with tuberculosis sanatoria, and ambitious and interested teachers are I believe attainable anywhere, and we of the National Association should make it our business to convince our general medical faculties of this fact.

We too must use our best efforts to arouse those whose special interests lie in other fields of medicine to the importance of the study of tuberculosis. We must show them that we believe that tuberculosis is vastly more than a particular affection of the lungs. We must do our work so that no orthopedist, no pediatrician, no urologist can afford to neglect it. We can learn much from them if we indicate to them research problems in their particular branches on which they can profitably work. But we should go about this, interested not too obtrusively in the National Association as such, but with our energies whole heartedly given to tuberculosis.

# THE MINERAL METABOLISM OF EXPERIMENTAL SCURVY OF THE MONKEY.

By C. P. Howard, M. D., and T. Ingvaldsen, M. Sc.,

*State University of Iowa, Iowa City, Iowa.*

In 1912 one of us published with L. Baumann [1] the mineral metabolism of a case of scurvy in an adult male. No further human cases having appeared in our clinic we next turned our attention to the study of experimental scurvy in the guinea-pig.[2] Realizing that the higher anthropoid apes and monkeys were more suitable to our purposes, we have spent the last year or two in studying the mineral metabolism of the monkey (Macacus rhesus). Strange as it may seem the earliest use of the monkey for this purpose was in 1900, when Jackson and Harley [3] fed one group with rice, corn and small amounts of fresh meat without the appearance of scurvy; a second group was fed with similar amounts of putrid meat without vegetables and a third group with similar putrid meat and vegetables. In both the second and third groups scorbutic symptoms were found. The authors concluded from this that the putrid state of the meat and not the insufficient quantity of the food was responsible for scurvy.

Twelve years later Carl Hart reported in a series of papers [4, 5, 6, 7] and finally in monograph form [8] anatomical studies of scurvy produced in monkeys. In five young monkeys fed on condensed milk and water for periods varying from two to four months there appeared a hæmorrhagic condition of the gums, loosening of the molar teeth, exophthalmos from intra-orbital hæmorrhages, œdema of the eyelids, subperiosteal hæmorrhages of the skull, a bloody diarrhœa, swelling of the epiphyses of the long bones and fractures of both humerus and femur. In addition, the radiograms showed the white line described by Fraenkel. In from one to two months from the onset of the symptoms death occurred associated with loss of weight, apathy and extreme sensitiveness to handling resulting in the "jumping-jack" phenomenon described by Heubner in the child. At autopsy Hart noted (1) hæmorrhages into the soft tissues and beneath the periosteum and into the marrow of all the bones, (2) degeneration of the marrow of the subchondral-diaphyseal border and (3) rarefication of the entire bone substance and abolition of the endochondral new bone formation. This resulted in the production of the "Gerüstmark" or the "framework marrow" of Schödel and Nauwerck, namely, a marrow consisting of mucoid or fibrous tissue, poor in blood-vessels. There was a persistence of the calcium at the endochondral ossification zone. Lastly there appeared an area of débris—the "Truemmerfeld Zone" of Fraenkel, which is responsible for the white line in the skiagram. One monkey, however, showed signs of typical rickets which Hart explains by suggesting a common cause for both rickets and scurvy, some individual predisposition determining which disease will develop. Four of the 10 monkeys developed neither scurvy nor rickets. One will readily recognize in this description the characteristic symptoms and post-mortem changes seen in the adult and in the infantile scurvy of man.

Hart's work was confirmed in this country in 1913 by F. R. Talbot, W. J. Dodd and H. O. Peterson.[9] One monkey showed typical clinical signs and a positive radiogram, but at autopsy the bones did not show any scurvy or rickets. Yet there can be no doubt that this animal was suffering from scurvy, since at autopsy there were other evidences of the disease.

In none of these publications was the metabolism studied. Inasmuch as the metabolism of the monkey approaches somewhat closely that of man we decided to repeat these experiments.

Our first animal was used to make certain that we could reproduce the disease in our laboratory.

EXPERIMENT I.—A female Macacus rhesus, 6 pounds 5 ounces in weight, was placed on September 25, 1913, in an Abderhalden metabolism cage and kept in a bright, sunny, well-ventilated laboratory. The animal was in the best of health and spirits. It was placed on a general diet of bananas, peanuts and milk. The meals were given at regular intervals by the same laboratory attendant. On November 1, 1913, after five weeks had elapsed, in which to enable it to become accustomed to its surroundings and during which time it had maintained its weight (6 pounds 3 ounces), it was placed on a quantity of a dried milk preparation (The Merrell-Soule Skimmed Milk Powder, Syracuse, N. Y.), sufficient for its caloric needs. She lost progressively in weight until by February 12, 1914, she had lost 1 pound 7 ounces; on that date it was noted that she looked ill, had a poor appetite and was listless, sitting quietly in the corner of the cage; there was evident disability of the left arm and left leg, the former she nursed and the latter she dragged; there was distinct desquamation of the face and trunk, but there was no evident affection of the gums and no external hæmorrhages. In spite of the continuation of the dried milk food the monkey gradually regained weight and the other symptoms subsided.

She was therefore placed on condensed milk (The Ferndale Evaporated Milk) on April 17, 1914, at which time she weighed 5 pounds. On May 4, 1914, there appeared ecchymoses around the orbits and in the floor of the mouth, and swelling and blueness of the gums became evident. It was again noticed that she was constantly nursing her left arm and wrist and that she was more emaciated (4 pounds 10 ounces). There was some looseness of the bowels, but no melæna or hæmaturia. A skiagram on May 8 was negative. On June 8, 1914, one of the lower central incisor teeth fell out and the ecchymoses of the eyelids were more evident; slight conjunctival hæmorrhages too were seen; she then weighed 4 pounds 6 ounces. She became more and more inactive and could not be handled without evincing pain. On July 7, 1914, blood appeared in the stools. On July 9, 1914, she was chloroformed and skiagrams were taken which revealed the typical white line at the epiphyses of the wrist-joints with separation of the epiphyses at the lower end of both femora. Her weight was now 3 pounds 6 ounces or a loss of 46.6% of the body weight.

*The autopsy* by Dr. C. E. Royce* on July 9, 1914, revealed crepitation of the right wrist-joint. The lower left central incisor was missing and all the central and lateral incisor teeth were loose and readily extracted. The gums were bluish red but not appreciably swollen. The large intestine showed numerous areas of hæmorrhage and ulceration. The other abdominal and thoracic viscera were normal. The sternum and costo-chondral joints were normal. The epiphyseal regions at both wrists and elbow-joints showed marked softening and subperiosteal hæmorrhage, while several of the synovial cavities were filled with a bloody fluid. The lower extremities were less affected.

*Microscopically.*—The characteristic changes were found in the bones, namely, hæmorrhage into the marrow which frequently was of the "Gerüstmark" type, changes in the calcifying zone and an absence of cells in the intertrabecular spaces of the epiphyses which were often filled with red blood cells, and spindle cells. The sections from the viscera were normal with the exception of those from the large intestine, which showed amœbæ in the deeper portion of the mucosa and those from the liver and kidneys which presented a granular degeneration.

*Anatomical Diagnosis.*—Scurvy, with hæmorrhage and softening of the bones of the shoulder and pelvic girdle (except the clavicles) and extremities and the upper and lower alveolar processes; granular degeneration of the liver and kidneys; amœbic colitis.

Having successfully reproduced in every respect the classical picture of scurvy in its clinical and pathological aspects we next turned to the study of the metabolism. As there were no data in the literature on the mineral metabolism of the normal monkey Baumann and Oviatt studied this in our second animal and published their results in a separate paper.[10] This second monkey was now submitted to the same conditions as the first and ran a similar course clinically and at autopsy showed the same changes.

EXPERIMENT II.—Macacus rhesus (male). This monkey was kept in the Abderhalden metabolism cage in the same laboratory from September 25, 1913, when it weighed 5 pounds 13½ ounces to January 21, 1915, when it weighed 6 pounds 3 ounces. It was then placed on a weighed diet of bananas and milk and the normal metabolism studied. On January 28, 1915, it was placed on a restricted condensed milk diet. It gradually developed loss of weight, loss of strength, bodily inactivity, alopecia, gingivitis, bloody diarrhœa and the other symptoms noted in the former experiment. On June 4, 1915, it was chloroformed, weighed and skiagraphed. The weight was now 4 pounds 8 ounces, a loss of 27.2% of the body weight. The skiagrams showed very definite white lines at the lower epiphyses of the tibiæ and radii, thinning of the bony tissue at the lower end of the humeri and femora with an increase in the density of the corticalis of all the long bones. (See Plates I and II.)

At the *autopsy* by Dr. C. E. Royce on June 4, 1915, there were noted alopecia over the thorax, swelling and hæmorrhages of the gums, and looseness of the incisor teeth. The lower ends of the radii and ulnæ were swollen and crepitated on pronation and supination. The thoracic and abdominal organs were negative except for an intussusception of the sigmoid and pallor and flabbiness of the heart muscle.

The fourth and fifth costo-chondral articulation on the right and the fifth and sixth on the left appeared redder than the others. The long bones of the four extremities showed even more marked changes than in the first experiment, brittleness being a marked feature, as well as separation of the epiphyses; subperiosteal and intra-articular hæmorrhages were frequent. The rami of the lower jaw showed marked superiosteal hæmorrhages and fragility. The scapulæ and pelvic bones were also affected.

*Microscopically.*—The picture was similar to that in the former experiment, only that the lesions were more marked, particularly in the bone-marrow which was everywhere replaced by a homogeneous material.

*Anatomical Diagnosis.*—Scurvy with hæmorrhage and softening of the bones of the girdles (except the clavicles) and the four extremities, as well as the upper and lower alveolar processes; granular degeneration of the liver and kidneys; intussusception of the sigmoid with suppuration and necrosis.

The methods of feeding and of collection of the urine and fæces have already been described.[10] We waited until the disease-picture was characteristic for scurvy before investigating the nitrogen and mineral metabolism. Three periods were studied, each period consisting of two consecutive days, except the third, when owing to the occurrence of diarrhœa or melæna two consecutive days feces could not be obtained. The third period therefore represents the urine and feces of two days nine days apart.

* We wish to express our thanks to Dr. C. E. Royce, pathologist to the University Hospital, for his interest and valuable assistance in the gross and microscopic study of our animals.

The methods of analysis were the same as those described before [10] except that the total sulphur and sulphur partition were estimated according to Drummond's [11] modification of the benzidine precipitation method of Raschig.

The *nitrogen* loss that occurred coincides with our findings in the guinea-pig. This and the high urea content of the blood found by Lewis and Karr [12] in scorbutic guinea-pigs possibly indicate an increased nitrogenous catabolism in experimental scurvy.

The *ammonia-coefficient* (4.2%) shows a slight increase above the normal figure (1.4%), but this is not to be considered indicative of an acidosis, especially when one bears in mind that the analyses were made several weeks after the collection of the urine.

The *sulphur* partition and balance are normal. It is of interest to note that the inorganic, ethereal and neutral sulphur formed 58.6%, 21.6% and 19.6%, respectively, in the scurvy period as compared with 60.9%, 16.9% and 22.2% of the normal period. These figures, then, are further confirmation of the difference in the sulphur partition of the monkey and that of man. It would be of interest to determine the sulphur partition of the urine of the higher apes.

*Chlorine.*—There is a tendency to chlorine retention, especially in the last period, when more than half of the ingested chlorine was retained.

The *phosphorus* metabolism was unusual throughout. The marked retention during the first two periods, followed by the relative high excretion in the urine during the third period, is difficult to explain.

*Sodium and Potassium.*—The retention of these elements during the third period parallels that of chlorine for this period.

*Calcium and Magnesium.*—Considerable quantities of calcium were ingested during the scurvy period and there was pronounced retention. During the previously reported normal period there was almost calcium equilibrium. The magnesium requires no comment.

TABLE I.

| May, 1915. | Volume of urine in c. c. | Weight of dry feces in gm. | Total nitrogen. | | | | Ammonia nitrogen of the urine. | Sulphur. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Intake. | Output. | | Balance. | | Intake. | Output. | | | | Balance. |
| | | | | Urine. | Feces. | | | | Inorganic. | Etherial. | Neutral. | Feces. | |
| 5 and 6... | 361 | 4.29 | 3.2060 | 3.0671 | 0.2566 | 0.1177— | 0.0809 | 0.1695 | 0.0858 | 0.0340 | 0.0251 | 0.0189 | 0.0057+ |
| 10 and 11... | 385 | 8.74 | 3.2060 | 3.4500 | 0.5227 | 0.7667— | 0.1721 | 0.1695 | 0.0868 | 0.0346 | 0.0305 | 0.0383 | 0.0207— |
| 15 and 24... | 242 | 9.36 | 3.2060 | 3.2586 | 0.5598 | 0.6124— | 0.1606 | 0.1695 | 0.0909 | 0.0285 | 0.0325 | 0.0410 | 0.0234— |
| Daily av'ge. | 164.3 | 3.73 | 1.6030 | 1.6293 | 0.2232 | 0.3495— | 0.0689 | 0.0848 | 0.0439 | 0.0162 | 0.0147 | 0.0163 | 0.0064— |
| | | | | | | | | Abnormal | 58.6% | 21.6% | 19.6% | of T. S. | |
| | | | | | | | | Normal.. | 60.9% | 16.9% | 22.2% | of T. S. | |

| May, 1915. | Chlorine. | | | | Phosphorous. | | | | Sodium. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. |
| | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | |
| 5 and 6..... | 0.6894 | 0.5146 | 0.0005 | 0.1743+ | 0.5686 | 0.0187 | 0.2188 | 0.3311+ | 0.2704 | 0.1855 | 0.0126 | 0.0723+ |
| 10 and 11..... | 0.6894 | 0.5929 | 0.0011 | 0.0954+ | 0.5686 | 0.0229 | 0.4458 | 0.0999+ | 0.2704 | 0.2227 | 0.0258 | 0.0219+ |
| 15 and 24..... | 0.6894 | 0.3089 | 0.0011 | 0.3794+ | 0.5686 | 0.1147 | 0.4774 | 0.0235— | 0.2704 | 0.0872 | 0.0276 | 0.1556+ |
| Daily average..... | 0.3447 | 0.2361 | 0.0004 | 0.1082+ | 0.2843 | 0.0260 | 0.1903 | 0.0680+ | 0.1352 | 0.0825 | 0.0110 | 0.0417+ |

| May, 1915. | Potassium. | | | | Calcium. | | | | Magnesium. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. |
| | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | |
| 5 and 6..... | 0.8981 | 0.7279 | 0.0528 | 0.1174+ | 0.7318 | 0.1307 | 0.2475 | 0.3536+ | 0.0699 | 0.0196 | 0.0247 | 0.0256+ |
| 10 and 11..... | 0.8981 | 0.7933 | 0.1080 | 0.0032— | 0.7318 | 0.1250 | 0.5041 | 0.1027+ | 0.0699 | 0.0178 | 0.0503 | 0.0018+ |
| 15 and 24..... | 0.8981 | 0.4576 | 0.1155 | 0.3250+ | 0.7318 | 0.1590 | 0.5399 | 0.0329+ | 0.0699 | 0.0199 | 0.0539 | 0.0039— |
| Daily average .... | 0.4490 | 0.3298 | 0.0490 | 0.0702+ | 0.3659 | 0.0691 | 0.2152 | 0.0815+ | 0.0349 | 0.0095 | 0.0215 | 0.0039+ |

## CONCLUSIONS.

The changes in the mineral excretion of the monkey during the scorbutic period are not sufficiently significant to admit of easy interpretation.

The marked loss of the various mineral substances encountered in previous experiments with man and guinea-pigs was not observed in the present series.

FIG. 1.

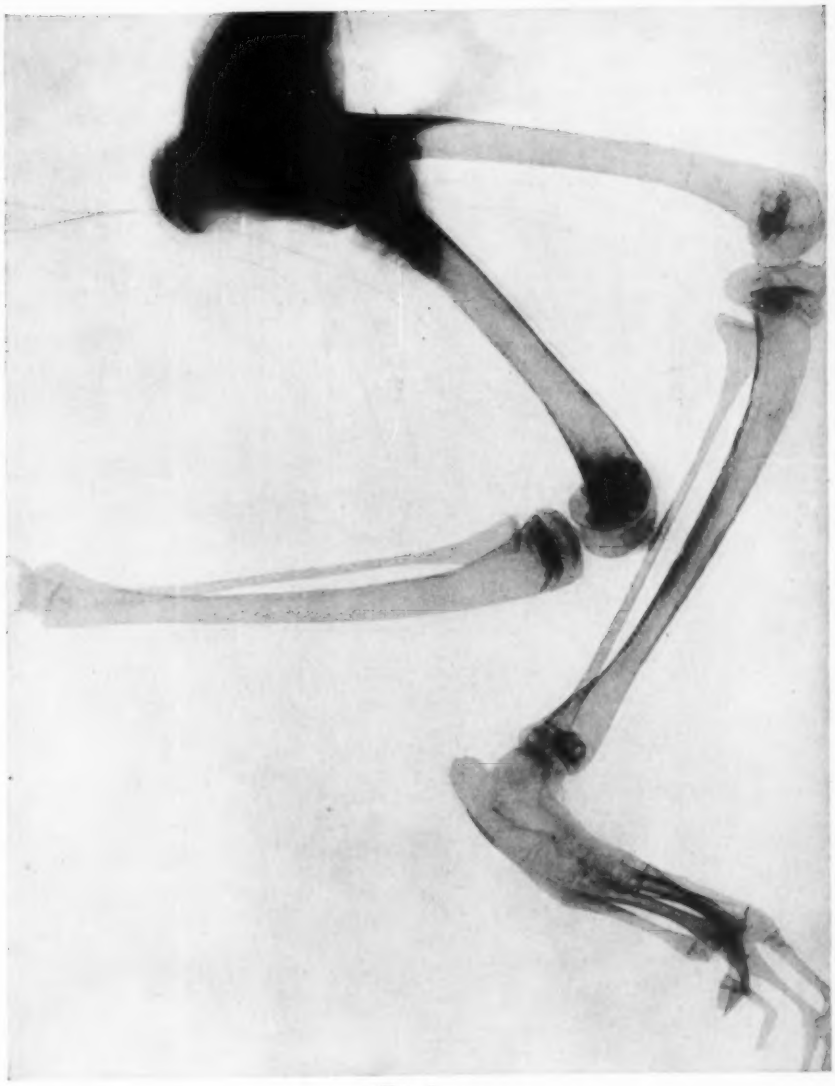

FIG. 2.

We conclude that a study of the intake and output of the inorganic elements in human adult scurvy and the experimental scurvy of the guinea-pig and the monkey does not yield sufficiently decisive information to warrant an explanation of the pathogenesis of scurvy.*

* We wish to acknowledge our indebtedness to Dr. L. Baumann, director of the Medical Research Laboratory, for many valuable suggestions.

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# JOHNS HOPKINS AND SOME OF HIS CONTEMPORARIES.[1]

By HENRY M. HURD, M. D.,

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The primary object of our Historical Club, when it was founded, was the study of medical history. To-night I have thought it wise to speak of the life of one who was not directly connected with the history of medicine, but who, because of the influence which the university and hospital he established have had upon medical education in this country, seems closely allied to medicine. I have also an additional reason for speaking briefly of his personal history before this club, because as the years pass I find that the career of Johns Hopkins becomes less familiar to the present generation, and there is danger that he may become a mythical personality. This is my reason for speaking of his origin and personal characteristics and giving some account of his career in Baltimore. I also wish to speak of his personal interest in the hospital and of the men he selected to carry out the enterprise.

According to an interesting research made some years ago by Miles White, Jr., a grandnephew of Johns Hopkins and at present one of the trustees of The Johns Hopkins University, the family of Johns Hopkins was of English descent, and came from England to Virginia about the middle of the 17th century. They were originally Puritans, driven from England by the persecutions to which they had been subjected prior to the accession of Charles II, and who had emigrated in company with many others of the same belief. They seem to have prospered for a time in Virginia, but were eventually compelled to remove to Maryland because of the restrictions placed upon them by the established church in Virginia, and also because there was great religious freedom in Maryland at that time.

The immediate ancestors of Johns Hopkins came to Maryland and settled in Anne Arundel County. Upon the Restoration in England, however, difficulties again arose, and again the Puritans were persecuted. Whether this had anything to do with their adoption of Quakerism I am unable to say. It is a fact, however, that Lord Baltimore, when his estates were restored to him after the Restoration by Charles II, showed great tolerance toward the Quakers; and it is to be remembered that in England the Quakers and Catholics seem to have been persecuted alike, which may have been one reason why Lord Baltimore showed the Quakers special consideration. At any rate, from the year 1700 on the Hopkins family were all Quakers. In Maryland two yearly meetings were established, one at West River, in the vicinity of Annapolis for the Western Shore, and the other at Third Haven, or Tread Avon, on the Tread Avon River near Easton, for the Eastern Shore. About 1671 Maryland was visited by George Fox, the founder of Quakerism, who is known to have attended the yearly meetings on both the Western and Eastern Shores. A few years afterwards William Penn also visited both meetings. The statement is made, as tending to show the good feeling between Lord Baltimore and the Friends, that on one occasion, accompanied by members of his family, he visited a yearly meeting in order to witness the manner in which services were conducted. It should be remembered that the Friends had a very remarkable influence in the development of the states of Pennsylvania, Maryland and Virginia, and in Maryland at once became a growing and influential body.

Johns Hopkins was born May 19, 1795, at White Hall, his father's estate near West River in Anne Arundel County. He was a son of Samuel Hopkins, who was a grandson of the first Johns Hopkins, whose mother was Margaret Johns and whose father was Gerard Hopkins, born in 1700, who was probably a son of an earlier Gerard Hopkins who came from Virginia. Samuel Hopkins was born in 1759 and died in 1814. He was a Quaker and a member of the meeting which met at West River. He was married, however, at Fairfax meeting in Loudon County, Virginia, to Hannah Janney in 1792. Hannah Janney was born May 19, 1774, and was the daughter of Joseph and Hannah Janney. Samuel Hopkins

[1] Read before The Johns Hopkins Hospital Historical Club, Monday, March 12, 1917.

seems to have been considerably older than his wife, who was married at the age of 18. To Samuel and Hannah Hopkins were born 11 children, 6 sons and 5 daughters, all of whom grew up. Johns Hopkins was the second son. Of Samuel Hopkins it is said that he was "an upright, noble-minded man, polite, agreeable and entertaining in conversation, much beloved by his friends and acquaintances, useful in society, his neighborhood and family." Of Hannah Janney Hopkins it is recorded that "she was a woman of superior intellect and will and one of the guiding spirits of the Baltimore yearly meeting." Later in life, after she came to Baltimore to live, she became a preacher in the Society of Friends.

Many interesting details are given concerning Johns Hopkins as a boy. The family lived liberally upon a large farm and seem to have prospered. At one time the possession of slaves had enabled them to cultivate the farm with ease and to engage especially in the cultivation of tobacco, which required much care and heavy work. For many years, however, the Religious Society of Friends had become very much interested in freeing the slaves and had borne constant testimony against the holding of men in bondage as entirely inconsistent with their ideas of right. In 1812 the yearly meeting adopted a minute that no persons could remain connected with the meeting who held slaves. It is said that Samuel Hopkins was much troubled by this action, in view of his large family and the difficulty of managing his estate without the aid of slaves. He walked the floor at night in his perplexity, and finally came to the decision that he ought to emancipate his slaves, which he did in 1812. Such action on his part he knew would give rise to much criticism from his neighbors who still held slaves and to a loss of prestige and influence in the community. It was also practically impossible to secure any labor other than slave labor, and the step necessitated great changes in the duties and responsibilities placed upon himself and his sons by compelling them to do the work of the plantation.

Tradition states that Johns Hopkins was in the habit of walking to school, in company with his younger brothers and sisters, a distance of two miles, and that he exercised a supervision over the other children and was in many ways regarded as a leader among them.

In 1812 he obtained a position in the store of his uncle, Gerard T. Hopkins, in Baltimore, where he was employed for several years. Gerard Hopkins was also a Friend and a preacher.

Baltimore, at that time a new city in Maryland, was a comparatively insignificant town. It was not incorporated as a city until 1796, when large additions were made to its limits, as is shown by the fact that in 1790 it contained 13,503 inhabitants, whereas by 1800 the number had increased to 31,514; by 1810 it had increased to 46,555, and by 1820 to 62,738. This indicates that Baltimore had a comparatively slow growth—about fifteen or sixteen thousand inhabitants in each decade. It was, however, a city of considerable commercial importance. Tobacco was extensively grown in Maryland, and Baltimore was the great shipping port for this product. It was also a shipping port for grain and flour to the West Indies and South America. Many of the streams, like the Patapsco, Jones's Falls and Gwynn's Falls, had large flour mills upon their banks run by water power, where wheat, then extensively grown in the region, was converted into flour. In many instances in order that the flour might be transported to South America in comparatively slow sailing vessels without danger of spoiling, bakeries were established in connection with flouring mills and a large proportion of the flour was baked into ship biscuit to supply these hot countries. There was also an extensive trade with the West Indies in sugar and with South America in coffee. During the Napoleonic wars there was also an extensive trade in neutral products with the European countries and particularly with the armies in Spain. The commercial activity of Baltimore, therefore, was very extensive. During the War of 1812 many of the sailing vessels, which operated between Baltimore and the Southern ports, were converted into privateers. In scanning the list it is apparent that more privateers sailed from Baltimore than from either New York, Philadelphia or Boston. The manner of life of the city itself was not unlike that of ordinary seaport towns. Very little was done in an educational way except by private initiative, and the same is true of philanthropic and charitable work. It was essentially a commercial city and its intellectual activity was largely in the line of business. It was a thriving, bustling seaport town, with many characteristics which had been derived from early settlers, who were largely from Scotland or the north of Ireland and engaged in commercial or shipping pursuits.

After five years of apprenticeship in his uncle's store Johns Hopkins established a grocery business for himself. His father died in 1814, and tradition states that at the time of his death several crops of tobacco had accumulated on the plantation near West River on account of the embargo of 1807, and these his mother, who managed the farm, sold at a good price at the close of the war and placed the money in his hands, for which he paid her interest, and which enabled him to begin business on his own account. We know little about his business habits, but it is evident that from the beginning he was an active, efficient and prosperous man. At first the firm was Hopkins and Moore. Subsequently two of his brothers and a cousin were associated with him. He does not seem to have had any domestic life until after 1832, when in consequence of an attack of cholera which nearly cost him his life he gave up living in a hotel on Baltimore Street and purchased a house on Franklin Street, which he occupied with his two brothers, one of whom was fatally injured in riots which disgraced Baltimore about 1835 by reason of the dissatisfaction of the populace with the failure of several important banks. The house on Franklin Street was occupied by Johns Hopkins until 1843, when his mother, failing in health, came with two of his sisters to reside with him, and a larger house was purchased on Lombard Street, where all lived until his mother's death in 1849. Mr. Hopkins then purchased the house immediately opposite the Hotel Rennert, which with his two sisters he occupied for the remainder of his life. About 1844

he purchased an estate known as Clifton. He rebuilt the house and made great improvements on the property, establishing greenhouses, planting trees and in many ways making it an ornamental park. For many years, in fact, it was the most conspicuous park in Baltimore and was regarded as a show place.

Johns Hopkins had only the education which was available at the country school in Anne Arundel County, but it must be borne in mind that the country schools in many parts of Maryland were superior to the schools which existed elsewhere. The prosperity of the colony, largely due to the sale of tobacco, early brought many Englishmen of excellent education to Maryland in search of fortune. Many of them had met the usual fate of such adventurers and were compelled to engage in teaching. There is a tradition that the school which Mr. Hopkins attended during his boyhood was taught by a scholarly man who had been a student at Oxford and was far beyond the ordinary average of teachers in country schools. The statement is also made that his father, Samuel Hopkins, was a man of much reading, who regularly supervised the education of his son, especially in the study of history, reviewing with him the work of the school at the close of every week in the presence of the family. It was the custom of Friends then and for many years afterwards to read the best books and to spend quiet evenings at home in reading and study. The library which Johns Hopkins bequeathed to The Johns Hopkins Hospital was an unusually large and well-selected one, particularly rich in historical and economic works. Johns Hopkins seems to have been all his life a diligent reader and to have profited by the knowledge which he obtained in this way.

His business training was acquired precisely as such training came to many other young men of the time. In the store of his uncle he performed the usual work, such as sweeping, unpacking goods and such general utility work as was then expected of all employees. It is evident from the accounts which are given that as long as he remained in business he was diligent as to hours and careful as to the extent of the responsibilities which he assumed. When he retired from business in 1847 he became connected with various large enterprises, such as banks, coal-mining companies and transportation companies, and was able by reason of his business experience, sagacity and intuitive perception of the character and possibilities of young men to give them timely pecuniary assistance. The statement has been made again and again by men who secured credit through his assistance, that they owed their ultimate business success to the help which he gave them. There are traditions that upon discount day at the different banks with which he was connected as director he often established the credit of comparatively unknown persons by affixing his personal signature to the paper of young men whose prospects of success were not apparent to his fellow directors, and that generally the men thus assisted became successful and prosperous business men, largely through the credit thus extended.

In the matter of personal character it is evident from the information which can be obtained that Mr. Hopkins was a man of large views and broad vision. He foresaw the importance to the city of Baltimore of the Baltimore and Ohio Railroad, and on two occasions advanced large sums of money, one to extend the railroad at an early date and the other to maintain its credit during the panic of 1873, when it was largely through his influence that Baltimore's credit was sustained and the city did not suspend payment of debts, as did many other cities. He arrived at his conclusions rapidly and intuitively, but his judgment was extremely sound. His physical health is said to have been not of the best, and following the attack of cholera in 1832 he suffered during the remainder of his life from insomnia and various digestive difficulties. The statement is made that the companionship of his favorite sister, who kept his house and looked after his diet and who always remained up at night until he returned home, to welcome him and talk over the affairs of the day, was of great service to him. He was fond of children, fond of his nieces and nephews, and given to hospitality. Religiously he was brought up in the Religious Society of Friends, but was not a member of the Society. He remained, however, essentially a religious man, and gave liberally to the support of the meeting, which he at times attended. His charities also were numerous, and at his death many old friends and business acquaintances were found by his executors to have been in receipt of regular allowances from him, of which the recipients alone knew the source. He was also generous to his relatives and friends.

He was unusually fond of country life, and at Clifton was able to gratify his taste by the improvement of his estate there. He planted the grounds with exotic trees of many rare varieties, had large and beautiful greenhouses, and indulged in the tastes which are available only to those who possess abundant means.

He was connected with many charitable and financial boards and assumed his share of the duties and responsibilities which attach to such work.

It is interesting to note that many persons have honestly thought they were influential in inducing Mr. Hopkins to devote so large a portion of his fortune to the establishment of the Hospital and University. It is evident that he had the matter much at heart, and was in the habit of talking with persons whose judgment he valued as to the disposition of his property. Francis T. King once said in a public address that Johns Hopkins had a strong conviction that his large fortune was given to him not for his own pleasure, but to accomplish some great work, and that it was his duty to make such use of his stewardship, as Mr. King expressed it, that it might continue to do good after his death. It is probable, therefore, that he conversed with many and received much advice. I have always believed that the example of George Peabody, of London, a former resident of Baltimore, who established the Peabody Institute and who devoted a large sum of money to education in the South, had great influence in leading Johns Hopkins' thoughts toward the establishment of an educa-

tional institution. The late President Gilman believed that several conversations held by Mr. Hopkins with Dr. Joseph Parrish, of Philadelphia, a member of the Society of Friends, had much to do with his ultimate design to establish a hospital and university. Dr. Parrish is reported to have said that as long as the world existed there would be sick people to care for and ignorant people to educate and that for this reason Mr. Hopkins would do well to establish a hospital and a university.

Johns Hopkins had perfected his plans a number of years before his death. Thus, he incorporated both the university and hospital in the year 1867, but neither institution had a full organization of its board until some years later. The original incorporators of the hospital were the following 12 named men, several of whom died before the formal organization of the board. These men were mostly business associates and personal friends of Mr. Hopkins or members of the Religious Society of Friends.

Francis T. King was designated by Johns Hopkins to be president of the board of trustees. Mr. King was a native of Baltimore, whose father came from England. He was educated at St. Mary's Seminary and had been engaged in various business enterprises. He was prominently connected with the Religious Society of Friends and for more than 20 years was clerk of the meeting. He was also interested in philanthropic enterprises, especially those in his own denomination. Later in life he occupied prominent positions in connection with two savings banks. He possessed energy, enthusiasm and great faith in the future of Baltimore. He had large plans, and with firmness of purpose and great patience was able to see most of them realized.

John W. Garrett, former president of the Baltimore and Ohio Railroad and a personal friend of Mr. Hopkins, was a man of great executive capacity and business ability. He was associated with Mr. Hopkins in many enterprises, and unquestionably had great influence with him. It is said he induced him to give a large sum of money to the Young Men's Christian Association to enable it to clear off the debt upon its building, at a time when Mr. Hopkins had lost several hundred thousand dollars in a mining enterprise.

Judge George W. Dobbin, who had been a judge of the superior court for a number of years, was an efficient member of the board. He was well known and respected for his probity, elevation of character and devotion to the public service. He served the university and hospital for many years and died at an advanced age, after the opening of both.

Galloway Cheston was a manufacturer, a member of the Society of Friends and prominent in financial circles in the city. He was a director of the Baltimore and Ohio Railroad, and a trusted associate of Mr. Garrett. His large fortune was acquired by the possession of flour mills, several of which were situated in the vicinity of Baltimore on Gwynn's Falls. He had excellent ideas as to organization and building and was personally interested in the plans of the hospital.

Thomas M. Smith was a merchant and a personal friend of Mr. Hopkins. His appointment seems to have been made because of his pleasing personality. I cannot find that he contributed in any great degree to the plans of the hospital.

William Hopkins was a cousin of Johns Hopkins and a merchant much respected.

Francis White had married a niece of Mr. Hopkins, and was one of the executors of his estate. He was also a trustee of the University. His services to the Hospital and the University were of great value and continued for many years. He had an attractive personality and made many friends. He lived to an advanced age and served both foundations faithfully and wisely.

Lewis N. Hopkins was a nephew of Johns Hopkins and had always been a great favorite with his uncle. He was a commission merchant, but during the last few years of his life was city collector. He had an intimate knowledge of his uncle's plans and was a trustee of both the Hospital and University.

Dr. Alan P. Smith was a grandson of Nathan Smith, who was a well-known physician in New England and whose life was spent in promoting medical education there. Nathan Smith was connected with four different medical schools, three of which he founded and in all of which he did very valuable work. His son, Nathan R. Smith, came to Baltimore, and was the leading surgeon in this city. Alan P. Smith, a son of the latter, was a surgeon of ability. He was the family physician of Johns Hopkins.

Dr. John Fonerden was the resident physician at the Maryland Hospital for the Insane, which stood on the site now occupied by The Johns Hopkins Hospital. Johns Hopkins was one of the board of visitors of this institution, and probably the association of the two in connection with the Maryland Hospital suggested his appointment as a trustee. He died prior to the organization of the board.

Charles J. M. Gwynn was a distinguished lawyer of Baltimore. He was counsel for almost all the large corporations of the city during some portion of his life. He was also the legal adviser of Mr. Hopkins, drew his will, and prepared the acts of incorporation of the Hospital and University. He served upon both boards faithfully for many years and both institutions owe much to his legal ability.

Richard M. Janney had married a sister of Johns Hopkins. He was at first a merchant and manufacturer, but during the last years of his life was occupied wholly in philanthropic work. He was much interested in the welfare of negroes who had been emancipated by their masters and who needed aid and education. He also took an active part in the establishment of schools for colored people at the close of the war and after their general emancipation. He was interested in the work of the Freedmen's Bureau in the South, and also was instrumental in establishing the Prisoners' Aid Society and a children's aid society, which afterwards became the Henry Watson Children's Aid Society. He, too, died before the Hospital board was organized. Mrs. Francis White was a daughter of Mr. Janney.

It is evident that these men were close acquaintances of Mr. Hopkins and familiar with his views and wishes as to the organization of the hospital. There is reason to think, from

John Hopkins

a careful reading of the letter prepared by him for the instruction of his trustees, that he had more definite views as to the organization of the Hospital than of the University. I have heard it said that the University trustees, in the organization of that institution, were often at a loss to know whether they were fully carrying out the will of the founder. In the organization of the Hospital there was, however, no reason for such apprehension. The clear-cut, enlightened and advanced views of Mr. Hopkins have served as a guide and have contributed materially to its advancement and prosperity.

# PRESENTATION OF THE MEDALLION PORTRAIT OF DR. RUPERT NORTON.[1]

DR. HURD: Our first duty to-night is to pay a tribute to a friend who we all loved and honored, and whose replica, which we shall see for the first time to-night, will always bring up many pleasant memories, and of course many sad ones. I think we can all rejoice that the affection of a devoted wife, together with the suggestions and recollections of relatives and friends and, above all, the expression of the artistic feeling of Mr. Victor Brenner, have reproduced our dear friend who has gone.

DR. W. S. THAYER: 'Twas an interesting group of men—the little family that constituted the House Staff of The Johns Hopkins Hospital during the years which passed before the foundation of the Medical School and before the days when we began to call on our own graduates to fill the interneships.

They were gathered from many schools—Lafleur and Hewetson and Barker and Cullen and Futcher and McCrae from Canada; Robb and Scott and Toulmin and Ghriskey and Farr and Bloodgood and Russell and Clark and Ramsay and Oppenheimer and Edwards from the University of Pennsylvania; Brockway and Parker and Lazear from New York; Nuttall and Blumer from California; Flexner from Louisville; Young and Huger and Block and Hoke from the University of Virginia; Councilman and Abbott and Clark and Reese and Baltzell and Simon and Hoch and Smith and Van Ness and Atkinson and Stokes and Walker from the University of Maryland; Phippin and Norton and Cushing from Harvard; Whitman from Paris; Broedel and Werckmeister from Germany—to mention only a part.

Few of us remain to-day to walk the familiar corridors, to keep alive the fading traditions and to welcome the old companions as they return from time to time from all parts of the world to edify us with their wisdom and, alas, to surprise us by their maturity. But there are some who come back to us often, who never change, whose eyes are as clear, whose step is as light, whose voices are as fresh as they were 25 years and more ago. Brockway and Scott and Reese and Hewetson and Livingood and Edwards and Oppenheimer and Ramsay and Lazear and Whitman—they can never grow old.

There is another, peculiarly dear to those of us who remain because we have of him a double memory—a memory of his youth in which he first left us, and of his prime in which we possessed him again.

Rupert Norton came to us in 1893 as a member of the Medical Staff, and remained with us for over two years. His work as a house officer was systematic, painstaking and thorough. As one reads to-day the records written in his neat and careful hand, the evidence of the character of his work is clear. Then came the years of his Washington practice, interrupted by the Spanish war, when he volunteered immediately as an acting assistant surgeon. At the end of the war came a period of years during which he was Medical Director of the New York Life Insurance Company in Paris, and then, in 1906, he came back to us again as Acting and Assistant Superintendent. From that time to the day of his death he devoted all his energies to the interests of the Hospital.

Among the past members of the staff few have been dearer to their associates. Norton was not one of those who made friends at first glance. He was so modest, so retiring, so diffident that some who met him casually mistook his shyness for coldness. No one who met him for the first time could have fancied the depth of his feeling, the vigor of his enthusiasm, the inflexibility of his determination, the inherent courage of the man. But wherever Norton was closely thrown with anyone he left a friend, and usually a devoted friend. The warmth of friendship that he inspired was but a reflection of his own loyalty. He was one on whom his friends could depend wholly; and while with regard to himself misunderstanding or false report stirred him little, yet nothing was so sure to excite in him an immediate and almost fiery resentment as a misrepresentation or a slighting statement about a friend.

He recognized unfailingly and appreciated deeply real merit in whatever garb it was clothed, and he was remarkably tolerant of the failings and weaknesses of others. But he had little patience with snobbishness or pretence and he was quick to detect and resent insincerity or indirectness.

I have sometimes regretted that one possessed of such admirable qualities of the heart—qualities which so endeared him to his friends—should not have given more of his life to a practice in which this human influence might have made itself more widely felt. To those who knew him well the memory of these qualities is a very dear possession. Of his generosity I have spoken elsewhere. Not many, even among his closest acquaintances, realized the extent of his kindly charity.

During his later years in the Hospital his wise advice and counsel were much valued by all who surrounded him.

Few men are quite certain of themselves. However steadfast one may be in his highest aspirations, however deep one's devotion to principle, who, at the bottom of his heart, has not known a lurking anxiety lest, in the great emergency, his action might fall somewhat short of his ideal? He who has

[1] Johns Hopkins Hospital Historical Club, March 12, 1916.

witnessed the too common frailty of his fellows, how has he not meditated on what his impulse might be in the moment of supreme temptation or danger?

But there are some men who inspire their friends with a peculiar sense of stability and solidity; some in whom we cannot imagine a weak or a mean or a cowardly impulse; some men of whom we feel absolutely sure. Such a man was Norton, and of his life we may say in the words of the wise old philosopher: "*. . . . meliorem illi vitam reddidit quam accepit: exemplar boni viri posuit; qualis quantusque esset ostendit: si quid adjecisset, fuisset simile praeterito.*" (Seneca, Epistola 93.) ". . . . for he hath returned a better life than he received. He hath set downe the patterne of a good man: he hath shewed what an one and how great he was: if he had added anything, it had beene like unto that which was past." (Lodge's translation, London, 1614.)

It is well that we should seek to perpetuate the memory of such men—that we should endeavor in bronze, in marble or in color to fix the impalpable and elusive inspiration that emanates from their presence. For the face of a good man is a benediction. And Norton's presence is with us now. One who knew him and loved him well, Victor Brenner, the distinguished sculptor, has brought back his calm and dignified and thoughtful features. And Mrs. Norton, who has herself a double claim to our affection as a graduate of our own training school for nurses and as his wife, has asked me to present this medallion to the institution to which he gave the best years of his life.

So may his face and figure continue to look out upon those who follow us—the face and figure of one whom we who knew him, love to recall—as has been set forth upon this plate—as physician, counsellor and friend.

JUDGE HARLAN: Serious purpose, fidelity to duty and loyalty in service are splendid qualities, and it was these qualities that the trustees of The Johns Hopkins Hospital recognized as dominating the life of Rupert Norton while he was connected with this institution—a connection which was all too short, owing to his untimely and pathetic death. What has been so well said by Dr. Thayer in appreciation of the life, of the services and of the character of Dr. Norton has found, I am sure, a response in the hearts of all of us, certainly in the hearts of the trustees. It is my great privilege, Mrs. Norton, on behalf of the Board of Trustees to accept this beautiful medallion portrait of our friend and to say that it will be placed among our most prized possessions, in order that it may be, not only for us but for those who come after us, a perpetual memory of one who lived a life of usefulness to this institution, of loyal, devoted and helpful service. He won the regard of all; he won the esteem of many; he won the love of those who knew him best.

DR. WELCH: There seems little to add to the beautiful tributes that have already been paid to the memory of our dear friend Rupert Norton. Each one who has spoken had used one word, which I think expresses the characteristic that comes first to mind when we think of Rupert Norton. Anyone who is familiar with Josiah Royce's book on loyalty knows all that that characteristic signifies when it is applied properly to a human being. Rupert Norton was loyal to his family, to his friends and to his duty. He was loyal to the right as he saw it—and he saw it very clearly. Dr. Thayer called to mind the early group of enthusiastic young workers who came here at the opening of the Hospital and before the Medical School was opened, and Rupert Norton belongs in that most interesting and really remarkable group. They are all devoted to his memory, and among them I think he made some of the closest friends of his life. Almost the last words from him that appear in print—and it is something of a coincidence, I think, that they appear in the number of our BULLETIN which contains Dr. Thayer's "In Memoriam" to Rupert Norton—were spoken at a memorial meeting in honor of Dr. Billings, who was a close friend of Dr. Norton and who also belonged in that early group. In his tribute to Dr. Billings he has chosen to emphasize just those qualities which applied most surely to himself—he emphasized the real solidity and straightness of the man, the hatred of all shams, the really getting to the heart of things. Dr. Norton, I think, exemplifies also a characterization of the educated man that was made by a colleague—William James, a great philosopher—who speaks of the value of higher education to lead men to know what is good in life, what is good in persons, what is good in art and in literature.

Rupert Norton came from a family and an atmosphere which really constitute memories cherished by all of us in America, and which must have had a great influence upon him. He had an unostentatious exterior, a reserve that may at times have seemed brusqueness, but there was behind it, as there is often behind the outward demeanor of a reserved man, a heart all kindliness and generosity and a certain genius for friends and friendship, and he linked close to him the few who penetrated the outer shell and got to the heart of the man. He began his professional life on the resident staff of Dr. Osler's service, and later spent three years in professional life in Washington, during which period he contributed over half a dozen papers to different medical publications. He enlisted at the outbreak of the Spanish-American War, and served throughout in one of the southern camps. After the war he went to Paris, where he held a position as medical director of an insurance company. He returned to Baltimore in 1906, at the time when Dr. Hurd took his long and well-deserved vacation. It was then I came to know him best. I soon learned that here was a man faithful in the discharge of his duties, filling a difficult position and filling it well. I was impressed then with his courage, with his patience under difficulties and with his determination to do the best for the service of the Hospital and the patients. He remained with us until the time of his death, and I think we all came to hold him in the highest esteem, and those of us who knew him best continue to have a very deep affection for him. He wrote some valuable papers on hospital organization. In a word, I think we can say that he has made contributions to all the different aspects of his work, first as an interne, then as an expert in life insurance

MEDALLION PORTRAIT OF DR. RUPERT NORTON.
BY VICTOR D. BRENNER.

matters, and then as a trained superintendent of a hospital, contributions that were entirely creditable, and that he gave promise of additional contributions had his life been spared. Dr. Thayer has spoken for his friends; Judge Harlan has spoken for the trustees of the Hospital, and if I may be allowed I will speak for the older group concerned in the organization and planning of the Hospital. We too are proud of this younger group of men. We cherish the memory of men like Rupert Norton, and it is well that his memory should be cherished here where he spent the best part of his life. He would probably have been surprised to know that we would hold a memorial meeting for him here, but we love to hold it and we are very grateful indeed to you, Mrs. Norton, for giving us this great privilege.

DR. HURD: There is one aspect I think in which Dr. Norton was preëminent, and that is as a literary man. He had literary instincts, a literary facility, and he also had a remarkably quick judgment as to literary form and taste. I have always felt that eventually he might have filled a high place in medical journalism. Few are capable of doing medical journalism as it ought to be done. Within two or three weeks of his sad and untimely death I received word from two different quarters, from editors of journals, that they had been going to offer him an editorial position. One of them was the most important medical journal in the country. I am sure that had he lived he might have found a career in medical journalism which he would have enjoyed. His heart was in that sort of work and he did it exceptionally well.

# NOTE ON BOOKS GIVEN TO THE JOHNS HOPKINS HOSPITAL BY DR. HUGH H. YOUNG.

By C. W. G. ROHRER, M. D.

The publications on genito-urinary surgery and allied topics, donated by Dr. Hugh H. Young, to the library of The Johns Hopkins Hospital, comprise a total of 567 bound volumes, 35 dissertations, 17 monographs and 494 reprints. For convenience of reference, these books and pamphlets may be subdivided into the following groups:

Bound volumes, including text-books, treatises, atlases, descriptive and illustrated catalogues, biographical sketches of eminent surgeons, etc., 567.
German dissertations, 35.
Monographs (mostly French), 17.
Reprints, 494.

The splendid array of text-books and treatises forms by far the largest and most important part of the collection. It is interesting to note that in this group are contained a number of books of real historical value. One of the first is "A Treatise of Venereal Diseases," a quarto volume by John Astruc (1684-1766), translated from the last Latin edition and published in London in 1754. Another is "A Treatise on Gonorrhœa Virulenta and Lues Venerea," by Benjamin Bell (1749-1806), a two-volume work published in Edinburgh in 1793. A third is the interesting collection of "Letters Concerning the Diseases of the Urethra," by Sir Charles Bell (1774-1842), published in 1810.

The works of Jean Civiale (1792-1867), the celebrated French surgeon, who applied the process of lithotripsy to the destruction of urinary calculi, also grace this collection. Here, too, are found the "Observations on the Structure and Diseases of the Testis," by Sir Astley Cooper (1768-1841), a folio volume published in 1830 and embellished by 24 plates; and "A Practical Treatise on the Diseases, Injuries and Malformations of the Urinary Bladder, the Prostate Gland and the Urethra," by Professor Samuel D. Gross (1805-1884).

This collection also contains a splendid copy of "Practical Observations on the Treatment of the Diseases of the Prostate Gland," by Sir Everard Home (1756-1832), John Hunter's brother-in-law. Home's work consists of two octavo volumes illustrated by copper plates from drawings made by William Clift, Hunter's last apprentice.

A book by William Cockburn entitled "The Symptoms, Nature, Cause and Cure of a Gonorrhœa," is of especial interest. This book, published in London in 1719, is the first medical work in which a colored copper plate was used.

A reprint of two tracts by Jean Paul Marat (1744-1793), a French revolutionist, is an exceptionally rare production. The first is "An Essay on Gleets." These tracts were printed for private circulation only, the edition consisting of 84 copies. The complete works of Philip Ricord and of Sir Henry Thompson are also of unusual interest and value, both from a historical and a clinical standpoint. Ricord was the first to establish the duality of gonorrhœa and syphilis; Sir Henry Thompson was famous for his work on the prostate and on stone in the bladder.

Reference should be made to the several treatises on anatomy and surgery, especially those published early in the eighteenth century. For example, the collection contains a copy of William Cheselden's "Anatomy of the Human Body," to which is added "A Short Historical Account of Cutting for the Stone." Cheselden (1688-1752) was an eminent English surgeon and anatomist, whose dexterity in lithotomy excited the wonder of his contemporaries. He preferred the lateral operation, performing it in 54 seconds of time.

The different editions of the works of John Hunter (1728-1793), the founder of scientific surgery, are well represented. The works of Malgaigne and the more modern works of Guyon, both celebrated French surgeons, add much to its value. The works of American surgeons—Senn, Gross, Bumstead, Taylor and others—occupy conspicuous places in Dr. Young's collection.

The early volumes of several important journals have been added: Annales des Maladies des Organes Génito-Urinaires,

Vols. I-XXI, 1883-1903; Association Française d'Urologie, Vols. I-XI, 1896-1907; Internationales Centralblatt für die Physiologie und Pathologie der Harn- und Sexual-Organe, Vols. I-X, 1889-1899; Centralblatt für die Krankheiten der Harn- und Sexual-Organe, Vols. XI-XVI, 1900-1905; Monatsberichte für Urologie, Vols. VI-XI, 1901-1906.

Mémoires de l'Académie Royale de Chirurgie, Vols. II, III, VI-XV, 1771-1774, and A Descriptive and Illustrated Catalogue of the Calculi and Other Animal Concretions Contained in the Museum of the Royal College of Surgeons in London, 1842-1845, Supplement I, by Thomas Taylor, 1871, 3 vols., should be also mentioned.

Several important works on anatomy have been included. Among these is the American edition of John and Charles Bell's treatise entitled "The Anatomy of the Human Body," a famous English text-book originally published in four volumes.

Among works of a biographical nature, in Dr. Young's collection, we find a copy of "Sketches of the Character and Writings of Eminent Living Surgeons and Physicians of Paris." Translated from the French of J. L. H. Peisse by Elisha Bartlett, M. D., it was published in Boston in 1831. The book contains nine biographical articles, beginning with Dupuytren and ending with Civiale.

A similar but larger work, appearing 12 years later (1843) than Peisse's book, has also been added. It is Dr. F. Campbell Stewart's volume, entitled "The Hospitals and Surgeons of Paris. An Historical and Statistical Account of the Civil Hospitals of Paris; with Miscellaneous Information, and Biographical Notices of Some of the Most Eminent of the Living Parisian Surgeons."

## BOOKS GIVEN TO THE JOHNS HOPKINS HOSPITAL LIBRARY BY DR. HUGH H. YOUNG.*

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Prostitution considered in its moral, social and sanitary aspects, in London and other large cities and garrison towns. 2. ed. London, 1870. 8°.
The functions and disorders of the reproductive organs. 6. ed. Phila., 1875. 8°.

AMBARD, L.
Physiologie, normale et pathologique des reins. Paris, 1914. 8°.

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A list of fellows. Chicago, 1913. 8°.

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Vols. 1-5, 1904-1909. New York. 5 vols. 8°.

AMERICAN MEDICAL ASSOCIATION, TRANSACTIONS.
Section on genito-urinary diseases. Chicago, 1914-1915. 2 vols. 8°.
Section on surgery. Chicago, 1914. 8°.
Section on surgery and anatomy. Chicago, 1903-1912. 10 vols. 8°.

ANNALES DES MALADIES DES ORGANES GÉNITO-URINAIRES.
Vols. 1-14, 16-21, 1883-1896, 1898-1903. Paris. 20 vols. 8°.

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Vols. 31-43, 1900-1906. Phila. 13 vols. 8°.

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ASSOCIATION FRANÇAISE D'UROLOGIE.
Vols. 1-11, 1896-1907. Paris. 11 vols. 8°.

ASTRUC, J.
A treatise of venereal diseases. Transl. from the last Latin ed. printed at Paris. London, 1754. 4°.

BAILLIE, M.
A series of engravings, accompanied with explanations, which are intended to illustrate the morbid anatomy of some of the most important parts of the human body. 2. ed. London, 1812. Fol.

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Genito-urinary diseases and syphilis. 2. ed. London, 1914. 8°.

BARTHOLOW, R.
Spermatorrhœa; its causes, symptoms, results and treatment. 4. ed. New York, 1879. 8°.
A practical treatise on materia medica and therapeutics. 7. ed. New York, 1893. 8°.

BASTIANELLI, R.
Studio etiologico sulle infezioni delle vie urinarie. Roma, 1895. 8°.

BAZY, P.
Maladies des voies urinaires. Séméiologie. Paris [n. d.]. 16°.

BEALE, L. S.
Urinary and renal derangements and calculous disorders. Phila., 1885. 12°.

BELHOMME, L., and MARTIN, A.
Traité pratique et élémentaire de pathologie syphilitique et vénérienne. Paris, 1864. 16°.

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A treatise on gonorrhœa virulenta and lues venerea. 2 vols. Edinburgh, 1793. 8°.

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Letters concerning the diseases of the urethra. London, 1810. 8°.
The same. Boston, 1811. 12°.
A treatise on the diseases of the urethra, vesica urinaria, prostate, and rectum. London, 1820. 8°.
Illustrations of the great operations of surgery, trepan, hernia, amputation, aneurism, and lithotomy. London, 1821. 4°.

BELL, J.
Engravings of the bones, muscles and joints. First Am. from the second London ed. Phila., 1815. 4°.

BELL, J. and C.
The anatomy of the human body. 4 vols. in 2. New York, 1809. 8°.

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Traité de la cystotomie sus-pubienne. Paris, 1827. 12°.

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A text-book of operative surgery. Phila., 1903. 8°.

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Anatomisch-chirurgische Abbildungen nebst Darstellung und Beschreibung der chirurgischen Operationen nach den Methoden von v. Graefe, Kluge, und Rust. Berlin, 1827. Fol.

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Orthopedic surgery and other medical papers. Boston, 1900. 8°.

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A clinical manual of the malformations and congenital diseases of the fœtus. Transl. by G. Blacker. Phila., 1912. 8°.

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Erfahrungen über Syphilis. Stuttgart, 1875. 8°.

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Valeur de la néphrectomie dans la tuberculose rénale. Paris, 1912. 8°.

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Atlas d'anatomie descriptive du corps humain. 2. partie. Cœur, artères, veines, vaisseaux lymphatiques et aponévroses. Paris [1844]. 4°.

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Calculs de l'urèthre et des régions circonvoisines chez l'homme et chez la femme. Paris, 1869. 8°.

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Traité des maladies chirurgicales et des opérations qui leur conviennent. 4. éd. Paris, 1831. Vols. 8, 9, 10. 8°.

BREWER, G. E.
A text-book of surgery. New York and Phila., 1903. 8°.

BUMSTEAD, F. J.
The pathology and treatment of venereal diseases. 3. ed. Phila., 1874. 8°.

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Endoskopie und endoskopische Therapie der Krankheiten der Harnröhre und Blase. Tübingen, 1889. 8°.

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The anatomy of melancholy, what it is, with all the kinds, causes, symptoms, prognostics, and several cures of it. 3 vols. Boston, 1859. 12°.

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An essay on the venereal diseases which have been confounded with syphilis, and the symptoms which exclusively arise from that poison. Dublin, 1814. 4°.
An essay on venereal diseases, and the uses and abuses of mercury in their treatment. 2. ed. London, 1825. 8°.

* This list has been prepared in the library by Miss Minnie W. Blogg and her assistants, Miss Foster and Miss Ebaugh, whose efficient services are well known and appreciated by all connected with The Johns Hopkins Hospital and Medical School.

CARSON, J.
Illustrations of medical botany. The drawings on stone by J. H. Colen. 5 vols. Phila., 1847. Fol.

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Lehrbuch der Urologie, mit Einschluss der männlichen Sexualerkrankungen. Berlin und Wien, 1903. 8°.
A text-book of genito-urinary diseases, including functional sexual disorders in man. Transl. and ed. by C. W. Bonney. Phila., 1906. 8°.
The same. 2. ed. 1909.

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Le cloisonnement vésical et la division des urines. Paris, 1903. 12°.
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Traité des maladies des voies urinaires. Paris, 1841. 12°.
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CIVIALE, J.
Nouvelles considérations sur la rétention d'urine. Paris, 1823. 8°.
Parallèle des divers moyens de traiter les calculeux. Paris, 1836. 8°.
Traité de l'affection calculeuse, ou recherches sur la formation, les caractères physiques et chimiques, les causes, les signes et les effets pathologiques de la pierre et de la gravelle [etc.]. Paris, 1838. 12°.
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Traité pratique sur les maladies des organes génito-urinaires. 2. ed. 3 vols. Paris, 1850-1851. 12°.
The same. 3. ed. 3 vols. Paris, 1858-1860. 8°.
Collection de calculs urinaires et d'instruments de chirurgie. Paris, 1869. 8°.
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# PROCEEDINGS OF SOCIETIES.

## THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

*FEBRUARY 5, 1917.*

**1. The Effect of Unilateral Excision of the Adrenal, Section of the Splanchnic and Section of the Renal Nerves, on the Secretion of the Kidney.** (Abstract.) E. K. MARSHALL, JR., and A. C. KOLLS.

This work was undertaken to study the effect of unilateral excision of the adrenal on the function of the kidney of the side operated upon. Dogs were used exclusively. Paraldehyde was used as an anesthetic except in cases of survival operations which were performed aseptically under ether. The urine was collected separately from each kidney by cannulating the ureters. The amount, specific gravity, chlorides, urea and creatinine of the urine were determined on each side during one-hour periods with and without diuresis. The excretion of phenolsulphonephthalein was determined on the two sides for one hour.

The results were as follows: The excretion of the kidney on the side operated upon as compared with that of the other kidney showed: increase of water, decreased specific gravity, relative decrease but absolute increase of urea, relative and absolute increase of chlorides, relative decrease but no absolute change in creatinine and phthalein. Removal of the adrenal in the dog is necessarily associated with injury to the splanchnic. Section of the splanchnic produces the same results as removal of the adrenal. However, this does not prove that the adrenal is not concerned, for one may argue that after splanchnotomy the adrenal ceases to secrete. Section of the renal nerves without disturbance of the relations of the adrenal and kidney causes the same changes as removal of the adrenal or as section of the splanchnic nerve.

The conclusion, therefore, seems justified that the changes are brought about by injury to the splanchnic nerve.

Some of the results are interesting in themselves. We can divide the substances excreted by the kidney into two classes: (1) Those that are excreted in increased amount after nerve section, namely, water, chlorides and urea; (2) Those whose excretion is unaffected by section of the splanchnic, namely, phthalein and creatinine.

Decreasing the blood flow of one kidney by careful compression of the renal artery causes: (1) In a normal animal a decrease of water, a relative and an absolute decrease of chlorides, a relative increase and an absolute decrease in urea, a relative increase but no absolute change in phthalein and creatinine; (2) In an animal operated upon, a return of the excretion of the kidney operated upon to one approximating the normal excretion in water, chlorides, urea and creatinine. Therefore, since the same changes can be produced by altering the blood flow through the kidney as are evident after nerve section, one must conclude that the phenomena obtained after splanchnic section are caused in part, if not entirely, by vasomotor disturbances and a consequent increased blood flow through the kidney of the side operated upon.

The results which have been given above have been obtained with hypertonic sodium chloride as the diuretic. A different picture is obtained when certain other diuretics are used. If after unilateral splanchnic section one employs sodium sulphate, sodium nitrate or urea in hypertonic solution as a diuretic, the differences in the excretion of the two kidneys are absent or much less marked than without diuresis, or with sodium chloride diuresis.

**2. Experiences with Acoustic Tumors.** (Abstract.) DR. HARVEY CUSHING.

This was a report of some detailed studies of a series of 30 tumors of the nervus acusticus, usually incorporated in the group of so-called "cerebellopontile" tumors. In the series of 468

verified cases in the speaker's series, 8 per cent proved to be isolated tumors (neurofibromas) of the acoustic nerve. A historical summary of the past observations on these tumors was given with special reference to Cruveilhier's notable case.

The symptomatology of the tumors was described and emphasis was laid upon the importance of securing an exact chronology of the symptoms, for the majority of cases show inaugural symptoms referable to the 8th nerve. Attention was also called to the question of the Bárány reactions and of the changes in the temporal bone shown by roentgenological studies.

Chief stress was laid upon the peculiar and destructive pathological character of the tumors, which have been variously designated as endotheliomas or fibromas or gliomas, but which probably come from some congenital *Anlage* in the peripheral end of the acoustic nerve at its entrance into the internal auditory meatus. It is safe at present merely to designate them as acoustic tumors.

The operative features of these cases were described, and the speaker gave in some detail his preferential procedure with a bilateral exposure of the cerebellum and an extracerebellar approach to the tumor. The mortality of these operations in the past has been regarded as nearly 70 per cent, but in the series of operations which were reported it was much lower, about 12 per cent, owing to the fact that an intracapsular enucleation of the growth was performed rather than an attempted total extirpation.

## DISCUSSION.

DR. WELCH: I agree with Dr. Cushing that the pathological side is one of the most interesting aspects of his paper, and I think it is a contribution of the first rank. These tumors are presumably tumors which correspond to growths which in the ordinary peripheral nerves are variously called neurofibromata, false neurofibromata, pseudo-neurofibromata etc., but after all essentially very much the same *Anlage*. It is the determination of this which is the capital point to my mind that comes out from Dr. Cushing's paper. It seems at first glance very disturbing to have these various names, fibroma, fibro-sarcoma, endothelioma, etc. It seems that if one pathologist calls a tumor an endothelioma and another calls it a fibro-sarcoma, they are miles apart. It is a matter of trifling importance. I do not think this great variety of designation is a matter for very severe criticism. I judge that these cases described by Dr. Cushing are not true neuromata in any sense; indeed I think the name neuroma is somewhat objectionable, although rather an old name. As I said before, these tumors evidently belong in the same category as those loosely called neuromata, pseudo-neuromata etc., in the peripheral nerves. Dr. Cushing has thrown great light upon this subject to-night.

DR. HALSTED. (Abstract.): The most interesting part I think of this paper is that one can take out these tumors with practically no mortality. In Germany the most recent statistics (as late as 1915) give a mortality of from 75 to 80 per cent, and one surgeon had a mortality of 100 per cent with quite a large number of tumors. All this is particularly interesting to one who has watched the development of the surgery of the brain. The greatest exponent in our times, next to Dr. Cushing, was Dr. Horsley, a brilliant man and a very skillful operator.

These cases that Dr. Cushing has shown are all of large tumors. They are, of course, much the most interesting to show, but I should like to know if he has had some early cases, such as some the otologists have operated upon. The otologists do make a diagnosis of the acoustic nerve tumors very early and some of them have taken the translabyrinthine route. For these large tumors that would be impossible, but for the early cases the translabyrinthine route has been practised successfully quite a number of times. Five or six surgeon otologists have been most successful so far as the life of the patient was concerned. One of the German surgeons who had had a tremendous mortality from the approach Dr. Cushing describes, in the only case in which he made a translabyrinthine operation, had a success. All the others, although otologists, succeeded in removing tumors of the acoustic nerve without a single death. They were all small tumors and the diagnosis was made early. The superior petrosal sinus was wounded twice, but the bleeding was easily controlled by pressure. I wonder if Dr. Cushing has had any cases he could approach, or would favor approaching, by this particular route?

DR. G. J. HEUER: As Dr. Cushing has indicated, the attempt to enucleate tumors in the cerebello-pontine angle has been attended by a high mortality; and he has therefore been led to adopt a palliative rather than a radical procedure in the treatment of these lesions. By bisection of the tumor with removal of tumor tissue from within its capsule; in other words, by leaving that portion of the tumor in contact with the pons undisturbed, he has avoided injury to the pons and lessened the danger of respiratory paralysis. It is not an ideal procedure, for recurrence of the tumor is certain. Yet until earlier diagnosis and earlier operation make radical extirpation possible without too great danger to the patient, we should perhaps be content with it.

DR. BARKER: With regard to early diagnosis, ordinarily one has to deal with pressure symptoms, deafness associated with tinnitus, or with dizziness or staggering. It seems to me desirable that practitioners should have the aid not only of trained neurologists, but also of a skilled otologist for special analysis of the cochlear and vestibular functions and particularly for the several Bárány tests.

What Dr. Cushing has said about the nature of these growths interests me very much. I think we ought to keep in mind the exact position of what we call the cochlear and vestibular nerves. These nerves do not correspond to peripheral spinal nerves in the ordinary sense at all, but rather to their posterior roots, since corresponding to the posterior root ganglia of the spinal nerves are the ganglion spirale and the ganglion vestibulare of the labyrinth. When we recall the histogenesis of the posterior root ganglia and remember that the ganglia of the cerebral nerves have a similar origin, you will understand that there can easily be in the posterior root ganglia, and also in the nerves between them and the central organ, structures that correspond to the framework of the central system. In this framework there are two main types of cells, the spongioblast type and the pure neuroglial type. The pictures Dr. Cushing has shown are suggestive to my mind of the possible presence of both types of framework cells in these growths, not unlike those occurring in retinal gliomata. Dr. Councilman has also apparently seen true glial fibers in these tumors.

DR. CUSHING: As Dr. Halsted says, the translabyrinthine operation was originally proposed by Panse and five or six operations have subsequently been attempted. It seems to me that there are obvious drawbacks to this method of approaching the lesion, for it is evidently suitable only for very small tumors largely limited to a dilated porus internus. Moreover, the procedure leaves no decompression area which could offset the possibility of future growth of an incompletely removed tumor. It is inevitable, too, after such an operation that there should be a subsequent cerebrospinal fluid leak, and a good chance, therefore, of meningitis. The operative wound in cases of a brain tumor should unquestionably always be closed without drainage.

Then, too, the difficulty of making a diagnosis before you have something more than a disturbance of vestibular function with increasing deafness is very great. Few people would be willing at this early stage to submit to an operation of such magnitude as the translabyrinthine operation. It is too heroic a procedure for the existing symptoms at the time when it offers a possibility of success.

I do not believe that a surgeon is likely to expose an acoustic tumor, except as an accidental finding, of such a size that it can be

totally enucleated, though Dr. Heuer tells me that you have had such a case here. The true acoustic neurofibroma cannot be enucleated as can the pseudo tumors of the peripheral nerves, and in attempting a complete enucleation the facial must necessarily be sacrificed together with the remains of the acusticus.

The enucleable tumors, in my experience, are tumors which do not arise from the nerve but rather from the meninges, pressing the nerves of the recess, the acusticus included, off to one side. These tumors are fibro-endotheliomas and are easily shelled out, though their removal is not absolutely total, for one is bound to leave the stalk of attachment, which offers a possible source of a recurrence of the growth. I have had some 60 of these tumors, several of them arising from a point which might have made them simulate an acoustic tumor, and it is important that they should be clearly distinguished from one another.

I am sorry to say that as yet the Bárány tests do not help us materially in arriving at a diagnosis, though they are interesting, of physiological importance, and should be carried out in all cases, if for no other reason than to improve our knowledge of vestibular function.

In regard to the pathology of these lesions, we had little idea, until we had assembled the entire group of 30 tumors, how very similar they were. Just what they ought to be called is not clear, and it is for this reason that I have accepted the non-committal term of "acoustic tumor." Possibly neurofibroma would be the best designation, though many of the tumors in the series had been called endotheliomas by numerous pathologists in the past. Some of the peripheral tumors in cases of von Recklinghausen's disease have practically the same architecture and are evidently lesions which arise from the same or a very similar *Anlage*.

*FEBRUARY 19, 1917.*

1. **Medical and Other Studies in the East Indies.** Dr. W. C. MacCallum.

## THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

*FEBRUARY 12, 1917.*

1. **Elizabeth Fry, Quaker Philanthropist: Her Work for Prisoners and Insane.** Dr. Henry M. Thomas.

   To appear later in the Bulletin.

2. **Thomas Holley Chivers, Medical Poet, Contemporary of Poe.** Dr. Thomas R. Boggs.

## THE LAENNEC SOCIETY.

*FEBRUARY 26, 1917.*

1. **The Complement Fixation Test in Tuberculosis with Besredka's Antigen.**[1] Dr. J. Bronfenbrenner.

Referring to the value of auscultation as an aid in the early diagnosis of tuberculosis, Laennec wrote in the preface to his great work, "I may say that no one who has made himself expert with this method will have occasion to say with Baglivi, 'Oh, how difficult it is to diagnose the disease of the lungs!'"

In spite of the great contribution rendered by Laennec himself, in spite even of the epochmaking discovery of Koch, the early diagnosis of tuberculosis is still a problem to be solved, even as it was one hundred years ago in the days of Laennec.

The difficulties confronting the students of tuberculosis are many; but the problem especially is difficult because of the extreme pleomorphism of the clinical manifestations of tuberculosis and because of the peculiar lack of uniformity in the course of this disease in different individuals affected, depending on their susceptibility or individual resistance, which are often subject to temporary fluctuations.

Although methods for the early diagnosis of tuberculosis are still wanting, the wide distribution of this disease is fairly well established. In fact, tuberculosis, not unlike syphilis, must be constantly kept in mind in making a diagnosis, whatever may be the clinical picture of the case.

Unfortunately, the manifestations of syphilis are no less pleomorphic than those of tuberculosis and in many instances they may amazingly simulate the clinical picture met with in tuberculosis. In cases where material for the bacteriological diagnosis of tuberculosis is not at hand, the Wassermann reaction is practically the only method for the differential diagnosis in such instances. However, as the Wassermann test itself is not absolutely specific, and as, on the other hand, it is not always present even in cases with definite signs of lues, this test does not offer an absolute means of differentiation between the two conditions.

In the quest for a reliable method for a diagnosis of tuberculosis, numerous investigators repeatedly attempted to apply the new methods used in the diagnosis of other infectious diseases, but their attempts were crowned only with partial success. Thus the use of agglutination, precipitation, meiostagmin and epiphanin reactions was found to be of little diagnostic value. The remarkable usefulness of the Wassermann reaction especially stimulated the efforts of numerous investigators along the lines of the application of the Bordet and Gengon reaction for the diagnosis of tuberculosis. The earlier efforts in this direction were not very encouraging. This could be due to several causes. It is possible that (owing to the walled-off nature of the lesions and the slow process of the disease in certain cases) there may be none or a very small amount of immune bodies present in the circulation. Moreover, the concentration of circulating antibodies is subject to constant and quite marked daily fluctuation in the same patient. Besides, the antibodies in tuberculosis may not be of the nature of amboceptors to any great extent. Again, tuberculous amboceptor, as suggested by Davidowitch, may be more thermolabile than most others, and since complement deviation is usually performed with inactivated serum, the amboceptor may be largely destroyed in heating.[2] Thus the amount remaining in the serum may not be large enough to be detected even by the delicate method of complement fixation.

In addition to the difficulties due to the apparent peculiarity of the immune processes in tuberculous individuals and resulting variations in concentration of specific amboceptors, the lack of proper antigens seems to have been largely responsible for the irregularity in the results obtained by different authors in their study of the complement fixation in tuberculosis. A study of the literature on this subject reveals the fact that, of all the different antigens used, suspensions of living or dead bacteria were found most reliable; but even with such antigens, the results obtained were not entirely satisfactory. In 1913, Besredka succeeded in cultivating tubercle bacilli on an entirely new medium. The fact that on this medium the organism showed some hitherto unknown properties induced him also to try the antigenic properties of his new cultures for the complement deviation test. Successful results obtained by Besredka and Manoukhing in their preliminary experiments have since been fully confirmed in several laboratories. It has been found that complement deviation with Besredka's tuberculin gives a very high percentage (90-95) of positive results in cases of clinical tuberculosis and at the same time the occurrence of the reaction, in cases in which tuberculosis could not be detected clinically, is limited to less than 10 per cent. The antigen of Besredka consists of autoclaved filtered cultures of tubercle

[1] From the Research Laboratories of the Western Pennsylvania Hospital, Pittsburgh, Pennsylvania.

[2] It is known that about 50 per cent of hæmolytic amboceptor is destroyed by inactivation.

bacilli grown on a new liquid medium, composed of alkaline broth to which are added egg-white and egg-yolk.[3]

As this medium cannot be made in large quantities on account of its rapid deterioration and has to be made fresh every time, the composition of the antigen made from it may vary in different batches. First of all, the chemical composition of individual eggs, and the consequent variations in the amount of alkali necessary for suitable clarification, vary to a marked degree. Besides directly affecting the chemical composition of the antigen, these fluctuations in the medium may also at times enhance or inhibit the growth of bacteria and thus still further influence the respective values of different batches of tuberculin for complement fixation.[4]

Another important source of variation was found in the apparent strain specificity displayed by different tuberculous sera. It is easy to demonstrate that certain tuberculous sera may fix the complement in the presence of certain selected samples of Besredka and other antigens. Thus, among fifty cases of diagnosed tuberculosis, in eighteen only did we find fixation with every one of the three samples of Besredka's tuberculin. In twenty-six cases we obtained fixation with two samples out of three, and in two cases the fixation was obtained with one sample of tuberculin only.[5] That the selective fixation with different antigens is due to the strain specificity, and not to some technical error, is evidenced by the fact that in many instances, in which the sera were examined repeatedly, the results of such examinations invariably confirmed the selective tendency on the part of the sera.[6]

[3] This medium is made in the following way: The white and yolk of an egg are each diluted with 10 volumes of water and filtered through a hard paper (Chardin). The yolk solution is carefully clarified by the gradual addition of sodium hydroxide. Both solutions are autoclaved and kept separately. Just before using one mixes 10 volumes of the sterile alkaline veal infusion (prepared without peptone, salt or glycerin) with two volumes of the sterile egg-white solution and one volume of the sterile clarified egg-yolk solution. This mixture is put into sterile tubes and is used without further sterilization. As this medium deteriorates on standing, it should be made fresh each time. Our experience fully confirmed the statement of Besredka about the rapid growth of certain strains of tubercle bacilli on this medium. It is true not all the strains seem to grow with equal facility, but certain strains like H46 and H48 from Dr. Baldwin, H12, H29 and H31 from Dr. Theobald Smith, R3 from Dr. Paul Lewis, and H389 from Dr. W. H. Park showed very definite growth within the first few days after planting.

[4] This consideration should be given a great deal of attention, as some of the batches of antigen sent to us by Professor Besredka were more anticomplementary than others without being more antigenic. Hence it is necessary to vary the amounts of tuberculin used for the test with each batch of antigen.

[5] Among 4000 sera examined in collaboration with J. Rockman and M. J. Schlesinger, with a view of establishing the nature of these variations in the respective fixing power of different samples of Besredka's antigen, the reaction was found positive with one or more samples of this tuberculin in 232 instances. Each of the 232 sera thus selected was reëxamined with seven different preparations of tuberculin. We found that in 167 cases (72 per cent) out of 232, the fixation was obtained also with at least four antigens out of seven used. Out of the remaining 65 cases, in 23 at least two tuberculins fixed the complement and in 12 cases the crude tuberculin of the New York Board of Health was the only one confirming the results obtained with the tuberculin of Besredka. In 30 cases out of this total of 232 the fixation occurred only with the tuberculins of Besredka.

[6] The existence of strain specificity in tuberculosis may be one of the contributing factors in causing much variation in the results obtained by different investigators in the complement deviation test for the diagnosis of tuberculosis.

The greatest and most important source of variation in the antigenic value of different batches of Besredka's tuberculin lies, however, in another direction. Already in the beginning of the study it appeared that a number of sera giving a positive Wassermann reaction often also showed fixation with Besredka's tuberculin. As one could not find clinical evidence of tuberculosis in all of these cases, the first explanation for this coincidence of the two reactions naturally was that the sera of syphilitics, having a high lipotropic coefficient, also fixed the complement with the tuberculin of Besredka on account of lipoids contained in it. The study of a number of sera giving a positive Wassermann reaction with this point in mind showed, however, that the complement deviation test with Besredka's antigen is not lipotropic in nature. Whenever present in sera possessing high lipotropic properties it depends on the presence of a separate antibody having its own index different from the lipotropic index in the same serum. Moreover, when the serum deviates the complement in the presence of both Besredka's tuberculin and pure lipin antigen, each of the two antibodies can be exhausted from such serum independently of each other. On the other hand, Besredka's tuberculin can be freed of its lipins without losing its property to fix complement in the presence of tuberculous sera. The lipins may be extracted by fat solvents, but the easiest method was found to be that of separation of the protein fraction by precipitation.[7]

The presence in the same serum of the property to fix complement with both antigens independently can be reproduced in experimental animals. When present in human beings (as well as in animals), the lipotropic antibody disappears under salvarsan treatment, whereas the tuberculous antibody persists.

The high percentage of negative reactions among clinically non-tuberculous (92 per cent), together with the other proofs of the high degree of specificity of this reaction, seem to indicate that the comparatively frequent simultaneous occurrence of the complement deviation test with Besredka's antigen and the Wassermann reaction in syphilitics is not due to some technical error.[8]

In fact the study of a number of cases from this point of view brings out some very interesting statistics. Thus Jones,[9] subjecting to the Wassermann test 251 unselected cases coming to the public tuberculosis clinic, found that 73 among them had a positive Wassermann. In the series of 346 tuberculous inmates of the Boucicaut Hospital 19 per cent gave a positive Wassermann test, according to Letulle,[10] and of these only 10 individuals (out of 64 reacting) were aware of their syphilitic infection or had definite signs of it. Our own results as well as these and other similar observations of different authors, which have come to our attention since our earlier work was published, suggest that occurrence of the complement fixation with Besredka's antigen in the cases in which the Wassermann reaction is also present may be due to the fact that either syphilis as such, or the antisyphilitic treatment, markedly lowers the resistance of the patients so as to make them either more susceptible to new infection with tuberculosis or to render them less resistant against the progress of this disease previously contracted.

Some of the authors, it is true, did not find any high frequency of occurrence of tuberculosis among syphilitics (as interpreted by

[7] Such precipitation of the antigenic fraction of tuberculin also offers the possibility of using a standard number of units of antigen and thus eliminating variations due to the quantitative differences in specific properties of different samples of tuberculin, without increasing the chance of obtaining lipotropic reactions.

[8] In this connection see results of Fraser, who, using various antigens both containing lipoids came to the conclusion that sera of syphilitics often deviate complement in presence of tuberculous antigens (bacillary emulsions). Zeitschr. f. Immunitätsforsch., Orig., 1913, v, 20, p. 291.

[9] Jones: Med. Record, 1916, Sept. 2.

[10] Letulle: Bull. de l'Acad. de Méd., Paris, LXXVIII, No. 16, p. 589.

the complement fixation test). However, if one takes into consideration the class of patients upon which the test is performed, this discrepancy can be easily explained. In our series of syphilitics we dealt with patients of all ages, greatly exposed to infection with tuberculosis in their factory surroundings, and even more so in the unhealthy conditions of their lives in the slums. The material of Dr. Craig, who found less than 1 per cent of tuberculosis in luetics, for instance, consisted, on the contrary, of a group of young men of military age comparatively free from tuberculosis at the time of their admission to military service and who ever since their admission had been placed in exceptionally good hygienic conditions.[11] It seems, therefore, that for a non-selected group of patients (as represented, for instance, by the admissions to the general hospital or dispensary) the simultaneous occurrence of fixation with tuberculin and lipin is quite frequent and is due to the simultaneous coexistence of two diseases. Such a conclusion is apparently borne out by clinical observations of such men as Fournier, C. F. Marshall, Douty, F. H. Andrews, Sir Jonathan Hutchinson and others (see Oxford System of Syphilis, 1914, III, 197).

As for the percentage of the occurrence of the reaction in different stages of tuberculosis when a purified antigen of Besredka is used, we wish to present these approximate figures. First stage, 84 per cent; second stage, 94 per cent; third stage, 15.3 per cent; clinically non-tuberculous (controls), non-syphilitics, 5 per cent.

The question of the surprisingly low percentage of positive results in far advanced cases was especially investigated. In addition to the antigen of Besredka we examined a large group of such cases from Leech Farm, Pittsburg, with the antigens of Craig, Corper and Calmette and more recently also with the antigen of Miller. Although it was possible to observe a slight variation in the results obtained with the respective antigens, in general they reacted no better than that of Besredka.

As for the reason for this failure of advanced cases to give fixation there can be at least two offered tentatively; one is, that the resistance of the patient has been exhausted, there is no new antibody formation; and the other, that the circulating antibody is taken up as formed by the combination with antigen which may greatly increase during the last stages of the disease.

Although the results of experiments on animals in the case of tuberculosis can have only a relative value, the general tendency of the results also suggests that the concentration of circulating antibody depends on the degree of resistance of the animal. Thus, rabbits seem to develop antibody and show the fixation of complement if infected with the human strains of tubercle bacillus, but usually fail to fix complement when infected with bovine. In guinea-pigs the results are even more convincing. The animals give complement fixation already as early as the fourth or fifth day after infection, but uniformly fail to fix complement during the fourth to the sixth week of the disease.

Before closing I would like to give in brief the procedure followed in performing the test.[12]

Fresh serum is used, thus obviating the danger of destruction of antibodies due to heating. The human serum is titrated for the amount of complement present. Such titration is performed with washed human red blood cells which have been previously sensitized with one unit of amboceptor. (The antihuman hemolytic system is used to avoid the uncontrollable factor due to the presence in human serum of varying amounts of natural antisheep amboceptor.) At the same time guinea-pig serum is titrated for its complement content, using human erythrocytes sensitized with the same amount of amboceptor. In setting up the test one adds a sufficient amount of guinea-pig serum to bring up the amount of complement already present in the human serum to two units. The antigen is then added and the tubes are incubated. At the end of the incubation, erythrocytes sensitized with one unit of amboceptor are added and after another period of incubation the progress of hemolysis is noted. We found this method to be very sensitive, its delicacy being entirely due to the minute amount of complement available for fixation and the absolute control of hemolytic system. Another advantage is in the fact that by using active serum we do not miss weak cases, where heating would have destroyed the antibody. As for the antigen to be used in the test, although we found Besredka's antigen to give the best results, we must admit, that the preparation of antigen as suggested by Miller and Zinsser is much simpler and, if the results obtained with it are as good as those obtained with Besredka's tuberculin, it seems that such antigen might be more practical for use in the test.

It is evident that a successful application of the complement fixation reaction for the diagnosis of early tuberculosis is already at hand.

There is very little doubt but that fixation indicates active tuberculosis, especially, if the reaction remains positive when repeated at intervals. In arrested or cured cases the reaction eventually becomes negative. The value of the negative outcome of the test is only relative (as it is also in the case of the Wassermann reaction), inasmuch as in advanced cases it is negative as well. In such cases the absence of circulating antibody may indicate the failing of resistance.

**2. Complement Fixation in Tuberculosis.** (Abstract.) DR. H. R. MILLER.

The phenomenon of complement fixation probably depends upon the fact that when an inciting organism invades the living body a reaction takes place between the serum of the host and the organism itself. In nearly all bacterial diseases this invasion is marked by a struggle the clinical manifestations of which constitute the picture of disease, and by a production of immune bodies or so-called antibodies. These antibodies (and here the term is used to represent diagnostic bodies rather than agents of any protective character) can be detected or measured in the blood of the host. In tuberculosis the most hopeful studies have been in the field of complement fixation of these antibodies. Enough work has already been done by the earliest investigators to demonstrate the value of the complement fixation in tuberculosis as a measure for diagnosis and prognosis.

In the main the technique of the reaction generally employed varied but little from the original Wassermann test; the antigens used varied greatly, however. These fall into four chief groups: (1) antigens prepared from the whole tubercle bacillus or any of its allied acid-fast bacilli; (2) tuberculins used as antigens; (3) tubercle bacilli extracts or derivatives, and (4) tuberculous or normal tissues employed as antigens.

Very encouraging results have been published with antigens of the types of Group 1 and Group 2, notably by the English workers who tried bacillary emulsions and by Besredka and his followers who worked with Besredka's tuberculin or modifications of it. Antigens of Group 3 and 4 have not been, comparatively, as useful as those of Group 1 and 2.

In February, 1916, Miller and Zinsser published results with a simple antigen made by grinding live tubercle bacilli with

[11] As a characteristic example of another extreme, proving the importance of ascertaining the social status of the patients on whom such tests are performed with the view of drawing conclusions as to frequency and interdependence of these two diseases, I wish to quote from Dr. N. B. Potter's article the results of Dr. Tedeschi, who found in his 10 years' service as a physician in a prison that 70 per cent of the cases of pulmonary tuberculosis had developed upon a luetic soil. (Tedeschi: Studium, Napoli, 1910, III, 343-377.)

[12] A detailed discussion of the technique will be given in the April issue of the American Journal of Syphilis.

ordinary table salt, and then adding distilled water up to isotonicity. This preparation may be used as it is or killed. It has given, and still gives, good results. There seems to be practically no false fixation of luetic or normal sera. With this antigen the test is positive in the largest proportion of Stage I, Stage II, and Stage III patients, yet in a number of cases of undoubtedly active tuberculosis the reaction is negative. For all practical purposes, however, the test is not positive in non-tuberculous persons, and is nearly always negative in arrested or quiescent tuberculosis and in luetic patients as well. The reaction is, therefore, an indicator of the activity of disease and does not point to the mere presence of tuberculosis. It does not parallel the tuberculin tests.

It seems fair to infer that a positive fixation implies absorption from active disease. In general, a negative reaction, except in those comparatively few instances where active disease is already present, signifies the absence of an active tuberculous process in the body.

## DISCUSSION.

DR. PETROFF: The papers presented by Doctors Bronfenbrenner and Miller to-night were very interesting to me and important. Most of you know that this test has been revived in the last few years. The results obtained by different investigators in this country and abroad have justified drawing the conclusion that there is some value in the complement fixation test as performed to-day and that the clinician may be benefited by the test.

In the last few years several very good antigens have been introduced. Personally, I do not care what kind the other man is using. I am willing to discard my antigen for that which anyone else is using if it will give better results.

In my routine studies I have used three different antigens: (1) potato filtrate, which is similar to the bouillon filtrate of Denys and which is prepared from the filtrate of potato broth cultures; (2) sodium hydroxide extract of pulverized tubercle bacilli, and (3) methyl alcohol extract of dry pulverized tubercle bacilli. The potato filtrate and sodium hydroxide are my reliable antigens. The methyl alcohol antigen is at present only of experimental interest. After an extensive study of some 20 antigens, I came to the conclusion that there is no antigen which would act as a "shot-gun" preparation. If cases are not alive from a clinical standpoint, I do not see why they should be from a serological standpoint. I do believe in multiplicity of antibodies, and if there is multiplicity of antibodies there must be multiplicity of antigens. That is the reason why I use more than one antigen. We may obtain a positive reaction with the potato filtrate and not with the sodium hydroxide extract antigen, and vice versa. A positive reaction with either very likely means active tuberculosis.

Every patient admitted to the Trudeau Sanatorium is given the following tests and examinations: complement fixation, tuberculin skin test, X-ray and physical examinations. Every Monday we get together and the cases in question are discussed. If there is any discrepancy, such a patient is put on exercise which very often decides the question of active disease.

We have divided our cases into three main groups: clinically active, apparently cured and quiescent, and several minor groups. If we take the first two groups of cases which are classified from the clinical standpoint, namely the clinically active and the apparently cured, we find that the complement fixation test is positive in over 90 per cent of the active cases, and negative in approximately the same percentage of the apparently cured. This probably means that a positive reaction indicates an active disease.

However, there is a group of cases which puzzles the clinicians, and very often it will be found that not two of them agree about activity in such cases. Cases in this group are quiescent and are on the borderline dividing the active from the apparently cured. A case belonging to this group may give us a positive complement fixation to-day and a negative reaction a few days later, or vice versa. Mild or violent exercise may cause the appearance of the positive reaction in a case where the reaction has been negative. A positive or negative reaction does not mean anything when the test is done only once. The blood of such quiescent cases must be studied every month, and only then may the findings bear some weight.

The complement fixation and the tuberculin skin test do not correlate in the early stage of the disease. But as the disease progresses toward a fatal termination, they correlate.

There are some conditions which may bring about a positive complement fixation where on previous examinations the test has been negative. An apparently arrested case with a negative fixation will during a cold give a positive reaction. The same results may be found after a general tuberculin reaction.

Now, a few more words before I close. The test is simple and may be run parallel with the Wassermann test. Much more work must be done before we can say that it can be adopted as a standard test. The test is not infallible, and a diagnosis based only on this test, disregarding the X-ray and physical findings, is deceptive. We are not yet sure of our interpretation of the test. I believe that complement fixation as applied to tuberculosis is much more specific than the Wasserman test. It is a true antibody antigen reaction. But I must confess that we have not yet the ideal antigen. The complement fixation has been established as an important test, and its future depends on the standardization of the antigen.

DR. KRAUSE: It has always been the hope of Dr. Baldwin, who for 25 years has stood in the forefront of tuberculosis investigation in this country, that some one would give us some method, some short cut, which would show us the difference between what we call clinical tuberculosis and those tuberculous changes that need no treatment, which may go on without manifesting themselves or being brought to the attention of the patient. Anything that would do this would mark the greatest advance and as an event in the history of tuberculosis would be comparable to the discovery of the bacillus itself.

The great majority of people who become diseased with tuberculosis do not need a strictly laboratory diagnostic method to detect that they have tuberculosis. But there continues to be a large number of cases which are on the borderline; a number of cases for which we have practically no method of determining whether they need treatment or not. We may have our opinion about this, but when we see the results of hasty diagnosis of tuberculosis, when we see what the stigma may mean and how tuberculous people react upon their environment, we begin to have some respect for a diagnosis of tuberculosis. In those cases that may be called concealed, the more or less quiescent cases, complement fixation would be of tremendous value if it would diagnose them and if we were certain of what the reaction meant. In advanced cases we would not need it so much, unless we were sure that it had some prognostic value. In the manifestly active cases we would not need it. But it is just these quiescent cases that are the ones for which we must perhaps have some kind of test if we are to make any advance over whatever methods we now have. I confess that it has always seemed inconceivable to me that there could be any biological test that would serve as an index of shadings and changes of activity or inactivity that are so fine and delicate as those we meet with in tuberculosis. Infection a test may show, and we would expect that some tests might reveal the presence or absence of frank activity of disease, although I would have you remember that the most practical fixation test, the Wassermann test, tells us little more in practice than that a man is infected. It will not differentiate symptomatic or active syphilis from latent syphilis.

I believe that all the work now going on in complement fixation in tuberculosis shows this, that there are a great many different types of antigen which will tell us that tuberculosis is at

work in the body, probably causing symptoms. I do not think though that the time has arrived when anyone should diagnose a case of tuberculosis on a complement fixation test alone. Every clinic that can should work hard at this test and gather observations made on the blood of patients who are suffering from all kinds of maladies. In the last analysis the place to work out this test is on experimental animals. It is here that we need most work.

Dr. Bronfenbrenner: Unfortunately, I am not situated as Dr. Petroff. I have no clinical material within reach and very often I am unable to examine the case twice, unless going back to the same test tube. However, I am aware of the fact, noted by others, that there are daily fluctuations in the antibody concentration in the serum of tuberculous individuals. My results have been obtained mostly on material sent to me sometimes from New York, sometimes from Chicago and only occasionally have I had it on the premises. The results stated by me have been published and I wish to refer Dr. Petroff to these publications where he will find more detail.

I had also among my cases a few where the tuberculosis was quiescent, and the reaction was strong. Among the cases with positive reaction there were also a few cases in which no clinical tuberculosis was disclosed by the physician in charge. However, at least two such cases went to Saranac Lake, and the diagnosis of tuberculosis was confirmed there clinically.

As for the experience of Dr. Petroff with complement fixation in rabbits, which all fixed the complement, even the controls, I think he makes a mistake somewhere. True, the rabbit is not a very reliable animal for the study of experimental tuberculosis, nor for complement fixation work, but in performing a number of experiments one still can draw conclusion as to the general tendency of the results. In my experience, though the majority of rabbits infected with human tuberculosis gave fixation, those infected with bovine bacillus as well as control (normal) rabbits practically never gave fixation with lipoid-free antigen.

The question of the co-existence of syphilis and tuberculosis is very important. I wish to repeat that in the great majority of cases, where I found both reactions present, there was clinical support for such serological findings supplied sometimes before and at other times after the serological examination had suggested the need of more complete clinical examination of the patient.

As for the sensitized cells, they are prepared by preliminary incubation of a suitable amount of amboceptor with washed red cells in proper concentration. It is very important properly to titrate the amboceptor for such a sensitization, for the excess of amboceptor causes hypersensitization of cells and that in turn entirely changes the quantitative relations of reagents in hemolysis. The proper amount of amboceptor for sensitization is determined as follows:

Place in several test tubes varying amounts of amboceptor solution and bring up the volume of 0.8 c. c. with physiological salt solution, then add 0.2 c. c. of the 50 per cent suspension of washed human red blood cells. Incubate for one-half hour in the water bath at 37° C. shaking occasionally. This results in 1.0 c. c. of a 10 per cent suspension of red blood cells sensitized with varying amounts of amboceptor. At the end of the half hour allowed for sensitization, distribute 0.025 c. c. of fresh human serum (human complement) into as many test tubes as there are dilutions of amboceptor above, and bring up the volume in each of these tubes to 0.9 c. c. These tubes then each receive red blood cells sensitized with gradually decreasing amounts of amboceptor. (This is done by transferring to each of them 0.1 c. c. from the various tubes above.) We have then a series of tubes each containing 1.0 c. c. of 1 per cent suspension of blood cells sensitized in the presence of varying amounts of amboceptor, and 0.025 c. c. of human serum. Incubate them at 37° C. for one-half hour and read the amount of hemolysis in the tubes. The smallest amount of amboceptor which has sensitized 0.1 c. c. of 10 per cent red blood cells so that they are completely hemolyzed by 0.025 c. c. of fresh human serum constitutes one unit of amboceptor.

Dr. Miller: Although the subject in some ways seems more confused to-night than I had thought likely I believe there are certain things fundamental upon which we can all agree. This is a biological and not a mathematical test, and we must bear in mind that if it is helpful at all in detecting any number of cases, no matter how small, where the clinician has had trouble in diagnosis, it is worth while. We must also agree upon a uniform way of reading our tests. We must decide whether 4 plus means something or nothing. We must disregard a great deal of theoretical consideration and try to see if there is any practical value in this reaction. We should prepare as many antigens as possible and get at the data of their relative usefulness.

I think it is important not to use active serum. Very few, if any, antibodies are destroyed in the heating. In the Board of Health of New York City, for instance, it is a routine procedure to keep the already inactivated serums 12 to 14 days for retesting, if necessary. By simply reinactivating the serum the test holds just as well. It is well known to many serologists that serum will sometimes contain a great deal of natural antisheep amboceptor which may be absorbed by the addition of red blood cells. To avoid error it is desirable to reinactivate the supernatant fluid; the test will not be interfered with. I think, too, that in the use of active serum there lies the danger that with the employment of some kinds of antigens, a false fixation is possible. Inactive serum is preferred by most workers.

There does not seem to be a great deal of strain specificity. If the tubercle bacillus strain is good for antigen, one can definitely depend upon the strain and it will behave constantly and properly. For that reason, a single strain alone may give very satisfactory results. Polyvalent strains should be used, nevertheless. I think it is instructive to note that when one gets a positive result, in spite of clinical data and experiences, the same result is obtained with all antigens.

As for a relationship between positive Wassermann reactions and fixation with tuberculous antigen, in our laboratory we have not found cross fixation. The New York Board of Health sent us about 200 positive Wassermann sera, and we found them all negative but four; of these four two showed tuberculosis and in two the diagnosis was not excluded. We do not get cross fixation, nor do we, as a rule, get a positive reaction in normal patients, or in patients who have no tuberculosis. We do very occasionally get a positive fixation which we cannot explain.

It must be remembered that serologists have pointed out that the Wassermann reaction also fluctuates from time to time for the same patient, and also that we know very little about the underlying causes of the Wassermann reaction, for it is possible to obtain fixation of luetic sera with a great many different antigens: streptococci, colon bacilli, spirochætæ, various fat preparations, etc. It is my purpose to emphasize the need for continuing the work of cross fixation in tuberculosis and to point out that, after all, although it may at times appear to be not conclusive, it may, on the other hand, offer certain help. In a small percentage of positive cases the test is negative, but, after all, this may not invalidate the value of the reaction.

I would like to say a good word for the antigen we prepare and emphasize that it is worth using, because it is very simple to make; it requires no great preliminary preparations, its anticomplementary dose is far above the antigen dose, it keeps well and with it the results have not been inferior to those obtained with other preparations.

In conclusion, I think all the evidence points to the fact that the complement fixation reaction is a test that has come to stay.